PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 20 July 2000 (20.07.00)	
International application No. PCT/GB99/03666	**Applicant's or agent's file reference** 44.67810/003
International filing date (day/month/year) 05 November 1999 (05.11.99)	**Priority date** (day/month/year) 13 November 1998 (13.11.98)
Applicant PIENE, Jan, Yngvar et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

09 June 2000 (09.06.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia RANAIVOJAONA
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

COCKBAIN, Julian
Frank B. Dehn & Co.
179 Queen Victoria Street
London EC4V 4EL
ROYAUME-UNI

Date of mailing (day/month/year) 21 December 2000 (21.12.00)	
Applicant's or agent's file reference 44.67810/003	**IMPORTANT NOTIFICATION**
International application No. PCT/GB99/03666	**International filing date** (day/month/year) 05 November 1999 (05.11.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
NYCOMED PHARMA AS Sandakerveien 100C N-0401 Oslo Norway	NO	NO
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
NYCOMED PHARMA AS Drammensveien 852 N-1385 Asker Norway	NO	NO
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Christine Carrié
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

COCKBAIN, Julian
Frank B. Dehn & Co.
179 Queen Victoria Street
London EC4V 4EL
ROYAUME-UNI

NOTIFICATION OF THE RECORDING OF A CHANGE

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Date of mailing (day/month/year) 21 December 2000 (21.12.00)	
Applicant's or agent's file reference 44.67810/003	**IMPORTANT NOTIFICATION**
International application No. PCT/GB99/03666	**International filing date** (day/month/year) 05 November 1999 (05.11.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
PIENE, Jan, Yngvar Nycomed Pharma AS Sandakerveien 100C N-0401 Oslo Norway	NO	NO
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
PIENE, Jan, Yngvar Nycomed Pharma AS Drammensveien 852 N-1385 Asker Norway	NO	NO
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Christine Carrié
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
44.67810/003		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03666	05/11/1999	13/11/1998
International Patent Classification (IPC) or national classification and IPC A61K9/16		
Applicant NYCOMED PHARMA AS et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09/06/2000	12.02.2001
Name and mailing address of the international preliminary examining authority: Europ an Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Paloniemi Legland, R Telephone No. +49 89 2399 7315

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03666

I. Basis f th r port

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-20 as originally filed

Claims, No.:

1-21 as originally filed

Drawings, sheets:

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	15-21
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations
   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

R It m V

Reasoned statement under Article 35(2) with regard to novelty, inventive step r industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: EP-A-0 192 460 (DYNAGRAN) 27 August 1986 (1986-08-27)
D2: FR-A-2 724 844 (LABORATOIRE INNOTHERA) 29 March 1996 (1996-03-29)

Claim 1 is directed to a **process** for a preparation of an orally administrable calcium composition, comprising the steps of:
(i) obtaining a physiologically tolerable particulate calcium compound having a mean particle size in the range 3 to 40 μm, having a crystalline structure and having a surface area of 0,1 to 1,2 m^2/g;
(ii) mixing said calcium compound with a water-soluble diluent and an aqueous solution of a water soluble binder in a fluid bed granulation apparatus and drying the resulting mixture to produce a first **granulate**;
(iii) optionally mixing said first granulate with one or more further components to produce a second granulate; and
(iv) optionally compressing said first or second granulate to form tablets.

Document D1, which is regarded to represent the closest prior art, discloses a process for making the agglomerates from which tablets containing up to 75 % of active incredient are directly compressed. The process of D1 has the same steps as claimed in the process of claim 1 (p.7, l.19-p.9, l.2). Up to 76,6 % of calcium carbonate with a particle size of 3-10 μm as an active incredient is disclosed in Exp. XIII. D1 differs from the invention by having no specific surface area of calcium compound disclosed. The technical problem was to provide a process for calcium compounds with reduced bulk and with a calcium compound content in excess of 60 % by weight. The solution was the process according to claim 1.
D2 discloses a therapeutic composition and a process for it comprising calcium compound with the same surface area as claimed in claim 1 (Exp. 1; Scoralite 1B). The skilled person confronted with the above mentioned problem and equipped with the

teaching of D1 would have had motivation and technical guidance (D2) for modifying the process of D1 by taking the calcium compound of D2 (Scoralite 1B), since in need of calcium compound with particle size of 3-10 microns, and would have arrived at a process of claim 1. Further dependent claims 2-14 do not contain any features, which in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step. These claims merely contain features already known from D1-D2 or typical features generally known to person skilled in the art in the field of processing orally administrable pharmaceutical compositions. Thus the subject-matter of claims 1-14 does not involve an inventive step (Art. 33(3) PCT).

Claim 15 is directed to a **granulate** comprising a fluid bed granulation granulate product of a physiologically tolerable calcium compound, a water-soluble binder and a water-soluble diluent, said calcium compound having a mean particle size in the range 3 to 40 μm, having a crystalline structure and having a surface area of 0,1 to 1,2 m^2/g. Document D2 discloses a therapeutic composition comprising calcium compound (carbonate), lubricant (magnesium stearate), water-soluble diluent (xylitol/sorbitol), water-soluble binder (polyvinylpyrrolidone) and vitamin D as a further component (Exp. 1; claims 1-8; p.7, l.7-8). The used calcium carbonate is of same type (Scoralite 1B) as used in the examples of the invention, therefore having implicitly same mean particle size and surface area. Consequently, the subject-matter of claims 15-20 is not novel (Art. 33(2) PCT).

Claim 21 is directed to a **tablet** comprising a compressed granulate as claimed above containing: calcium carbonate, vitamin D_3, a lubricant, citric acid and an oligo-saccharide. D2, which is considered to represent the closest prior art, discloses in an Example 1 a tablet comprising most of the features of claim 21. The other features (citric acid and oligosaccharide) are also disclosed in D2 (Exp. 6) being therefore obvious for the skilled man to combine the latter with the former ones. Consequently the subject-matter of claim 21 does not involve an inventive step.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) and (iii) PCT, the relevant background

art has not been indicated in the description and no corresponding documents (D1, D2) have been cited.

The unit "kp" employed on page 14 has not additionally been expressed in terms of the units stipulated by Rule 10.1(a) PCT.

M·H

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
44.67810/003		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/ 03666	05/11/1999	13/11/1998
Applicant		
NYCOMED PHARMA AS et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/GB 99/03666

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 192 460 A (DYNAGRAN) 27 August 1986 (1986-08-27) claims 1-25 page 29; example 13 ---	1-4, 6-11, 15-18
Y	FR 2 724 844 A (LABORATOIRE INNOTHERA) 29 March 1996 (1996-03-29) claims 1-8 page 3; example 1 ---	1-21
Y	DE 196 17 487 A (MERCK) 6 November 1997 (1997-11-06) claims 1,2,5,7 page 3, line 43 - line 45 example 1 --- -/--	1-21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2000	10/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/GB 99/03666

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 487 774 A (BASF) 3 June 1992 (1992-06-03) claim 1 page 1, line 47 - line 49	1-21
P,A	EP 0 931 549 A (GERGELY, GERHARD) 28 July 1999 (1999-07-28) the whole document	1-21
A	DATABASE WPI Section Ch, Week 199311 Derwent Publications Ltd., London, GB; Class A,Page 96, AN 1993-088592 XP002129448 & JP 05 032554 A (TEIJIN), 9 February 1993 (1993-02-09) abstract	1-21

1

INTERNATIONAL SEARCH REPORT

[redacted]ation on patent family members

International Application No
[redacted]T/GB 99/03666

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 192460	A	27-08-1986	US	4684534 A	04-08-1987
			AT	66368 T	15-09-1991
			AU	584674 B	01-06-1989
			AU	5377286 A	28-08-1986
			CA	1256028 A	20-06-1989
			DE	3680930 A	26-09-1991
			JP	2540131 B	02-10-1996
			JP	61225119 A	06-10-1986
FR 2724844	A	29-03-1996	AT	177319 T	15-03-1999
			AU	3168395 A	09-04-1996
			CA	2200568 A	28-03-1996
			DE	29521515 U	05-06-1997
			DE	69508263 D	15-04-1999
			DE	69508263 T	04-11-1999
			EP	0785769 A	30-07-1997
			ES	2131845 T	01-08-1999
			FI	971188 A	20-05-1997
			WO	9609036 A	28-03-1996
			HU	77702 A	28-07-1998
			JP	10505850 T	09-06-1998
			NO	971356 A	21-03-1997
			PL	319585 A	18-08-1997
DE 19617487	A	06-11-1997	CN	1216919 A	19-05-1999
			WO	9741835 A	13-11-1997
			EP	0904059 A	31-03-1999
EP 487774	A	03-06-1992	AT	113202 T	15-11-1994
			DE	69013689 D	01-12-1994
			DE	69013689 T	02-03-1995
			DK	487774 T	21-11-1994
EP 931549	A	28-07-1999	NONE		
JP 5032554	A	09-02-1993	JP	2702325 B	21-01-1998

PCT ORGANISATION MONDIALE DE LA Bureau inte

DEMANDE INTERNATIONALE PUBLIEE EN VERTU DU TRA

(51) Classificati n internationale des brevets 6 : A61K 9/00 — A1

(11) WO 9609036A1

(43) Date de publication internationale: 28 mars 1996 (28.03.96)

(21) Numéro de la demande internationale: PCT/FR95/01053

(22) Date de dépôt international: 4 août 1995 (04.08.95)

(30) Données relatives à la priorité:
94/11381 23 septembre 1994 (23.09.94) FR

(71) Déposant *(pour tous les Etats désignés sauf US)*: LABORATOIRE INNOTHERA, SOCIETE ANONYME [FR/FR]; 10, avenue Paul-Vaillant-Couturier, F-94111 Arcueil (FR).

(72) Inventeurs; et

(75) Inventeurs/Déposants *(US seulement)*: MEIGNANT, Catherine [FR/FR]; 42-52, rue de l'Aqueduc, F-75010 Paris (FR). STENGER, Eric [FR/FR]; 10, avenue des Chardons, F-94800 Villejuif (FR).

(74) Mandataire: DUPUIS-LATOUR, Dominique; Cabinet Bardehle, Pagenberg & Partner, 7, boulevard de Sébastopol, F-75001 Paris (FR).

(81) Etats désignés: AU, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LR, LT, LV, MD, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, UA, UG, US, UZ, VN, brevet européen (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Publiée

Avec rapport de recherche internationale.

(54) Title: THERAPEUTIC VITAMIN-CALCIUM COMBINATION IN UNITARY GALENIC TABLET FORM, METHOD FOR PREPARING SAME AND USE THEREOF

(54) Titre: ASSOCIATION THERAPEUTIQUE VITAMINO-CALCIQUE SOUS FORME GALENIQUE UNITAIRE DE COMPRIMES, SON PROCEDE D'OBTENTION ET SON UTILISATION

(57) Abstract

A therapeutical combination including elemental calcium and at least one vitamin D as the combined active principles, and further containing at least one dry and wet binder combined in a synergistic amount with at least one diluent, at least one binder and at least one lubricant, at least one of said diluent and said binder being a sweetener. The ratio of elemental calcium to vitamin D, expressed in mg of elemental Ca per IU of vitamin D, is advantageously 1-1.5, preferably 1.2-1.3.

(57) Abrégé

Cette association thérapeutique comprend comme principes actifs associés du calcium sous forme élémentaire et au moins une vitamine D. Elle renferme en outre au moins un liant à sec et en milieu humide combiné en quantité synergique avec au moins un diluant, au moins un liant et au moins un lubrifiant, l'un au moins dudit diluant et dudit liant étant un édulcorant. Avantageusement, le rapport du calcium sous forme élémentaire à la vitamine D, exprimé en mg de Ca élément par UI de vitamine D, est compris entre 1 et 1,5, préférentiellement entre 1,2 et 1,3.

UNIQUEMENT A TITRE D'INFORMATION

Codes utilisés pour identifier les Etats parties au PCT, sur les pages de couverture des brochures publiant des demandes internationales en vertu du PCT.

AT	Autriche	**GB**	Royaume-Uni	**MR**	Mauritanie
AU	Australie	**GE**	Géorgie	**MW**	Malawi
BB	Barbade	**GN**	Guinée	**NE**	Niger
BE	Belgique	**GR**	Grèce	**NL**	Pays-Bas
BF	Burkina Faso	**HU**	Hongrie	**NO**	Norvège
BG	Bulgarie	**IE**	Irlande	**NZ**	Nouvelle-Zélande
BJ	Bénin	**IT**	Italie	**PL**	Pologne
BR	Brésil	**JP**	Japon	**PT**	Portugal
BY	Bélarus	**KE**	Kenya	**RO**	Roumanie
CA	Canada	**KG**	Kirghizistan	**RU**	Fédération de Russie
CF	République centrafricaine	**KP**	République populaire démocratique de Corée	**SD**	Soudan
CG	Congo			**SE**	Suède
CH	Suisse	**KR**	République de Corée	**SI**	Slovénie
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovaquie
CM	Cameroun	**LI**	Liechtenstein	**SN**	Sénégal
CN	Chine	**LK**	Sri Lanka	**TD**	Tchad
CS	Tchécoslovaquie	**LU**	Luxembourg	**TG**	Togo
CZ	République tchèque	**LV**	Lettonie	**TJ**	Tadjikistan
DE	Allemagne	**MC**	Monaco	**TT**	Trinité-et-Tobago
DK	Danemark	**MD**	République de Moldova	**UA**	Ukraine
ES	Espagne	**MG**	Madagascar	**US**	Etats-Unis d'Amérique
FI	Finlande	**ML**	Mali	**UZ**	Ouzbékistan
FR	France	**MN**	Mongolie	**VN**	Viet Nam
GA	Gabon				

Association thérapeutique vitamino-calcique sous forme galénique unitaire de comprimés, son procédé d'obtention et son utilisation

La présente invention concerne une nouvelle association thérapeutique vitamino-calcique, son procédé d'obtention et son utilisation.

On connaît de nombreuses associations vitamino-calciques pour combattre diverses maladies.

Les effets thérapeutiques liés à l'administration conjointe de calcium et de vitamine D sont bien connus, comme cela est relaté par exemple dans les articles de Marie C. Chapuy et coll. — Effect of Calcium and Cholecalciferol Treatment for Three Years on Hip Fractures in Elderly Women, *British Medical Journal*, 308, 1081-1082 (23 avril 1994), de Marie C. Chapuy et coll. — Vitamin D3 and Calcium to Prevent Hip Fractures in Elderly Women, *New England Journal of Medicine*, 327, 1637-1642 (3 décembre 1992) et dans l'article intitulé Supplementation with Vitamin D3 and Calcium Prevents Hip Fractures in Elderly Women, *Nutrition Reviews*, Vol. 51, 6, pp. 183-185.

Ces articles montrent également la variabilité des effets thérapeutiques de l'association en fonction du dosage de calcium et de la vitamine D, avec une dose journalière optimale se situant, pour une indication dans la prévention et le traitement de l'ostéoporose, aux alentours de 1000 à 1200 mg de calcium élément et 800 UI de vitamine D3.

Le calcium et la vitamine D sont généralement administrés au patient simultanément, mais sous des formes distinctes, par exemple des comprimés d'un sel de calcium et des gouttes de vitamine D.

En effet, les sels de calcium acceptables du point de vue pharmaceutique et la vitamine D présentent, chacun en ce qui les concerne, des caractéristiques très spécifiques du point de vue de la galénique (voir notamment le EP-A-0 413 828 qui concerne une préparation stabilisée de vitamine D3 destinée à potentialiser la stabilité du principe actif), ce qui conduit à un conditionnement sous des formes séparées.

Mais ceci rend difficile le respect des doses absolues et relatives de calcium et de vitamine D, et donc l'observance correcte du traitement, en particulier sur une longue période.

Il a été déjà proposé des associations calcium et vitamine D sous une même forme, par exemple par le WO-A-94 06435 (procédé de traitement gynécologique utilisant notamment une combinaison de vitamine D et de calcium), le WO-A-92 19251 (association de vitamine D avec du calcium pour combattre l'ostéoporose, plus particulièrement sous forme buvable), le EP-A-0 197 514 (composition pharmaceutique comprenant une hormone parathyroïde ou un fragment physiologiquement actif de celle-ci en combinaison avec de la vitamine D hydroxylée ou un sel de calcium non toxique pour augmenter la masse osseuse) ou encore le DE-A-42 12 122 (élément basse calorie à base de protéines, d'un sel de calcium et de vitamine D).

Mais dans ces formes connues les proportions entre calcium et vitamine D sont généralement assez éloignées des proportions optimales souhaitables indiquées notamment dans la littérature précitée.

Ces formes connues correspondent d'ailleurs souvent plus à des suppléments vitamino-calciques (suppléments alimentaires ou spécialités "OTC" vendues sans prescription médicale) qu'à de véritables spécialités pharmaceutiques à visée thérapeutique destinées à prévenir ou traiter des affections telles que l'ostéoporose avec une posologie précise.

Il existe ainsi à l'heure actuelle un besoin de pouvoir disposer d'une association vitamino-calcique comportant, sous une seule et même forme, un dosage relatif optimal entre calcium et vitamine D, tout particulièrement pour la prévention et le traitement de l'ostéoporose.

Mais du fait de la nature des sels de calcium disponibles acceptables du point de vue pharmaceutique, il est relativement difficile d'associer du calcium sous forme élémentaire avec de la vitamine D dans certains dosages spécifiques. Ceci est particulièrement vrai si l'on désire obtenir des comprimés par un procédé de fabrication par compression directe. Les contraintes des principes actifs, à savoir le calcium sous forme élémentaire et la forme de vitamine D, ne permettent alors pas une mise en oeuvre directe.

La présente invention résout les problèmes mentionnés ci-dessus en proposant une association thérapeutique vitamino-calcique sous forme galénique unitaire de comprimés, comprenant comme principes actifs associés du calcium sous forme élémentaire et au moins une vitamine D, caractérisée en ce qu'elle renferme, en outre, au moins un liant à sec et en milieu humide combiné en quantité synergique avec au moins un diluant, au moins un liant et au moins un lubrifiant, l'un au moins dudit diluant et dudit liant étant un édulcorant.

La présente invention a également pour objet un procédé d'obtention d'une association thérapeutique vitamino-calcique comprenant du calcium sous forme élémentaire et au moins une vitamine D, qui est caractérisé en ce qu'il consiste : (a) à granuler le calcium sous forme élémentaire avec un liant à sec et en milieu humide ; (b) à prémélanger la vitamine D avec un liant édulcorant dans une étape séparée ; (c) à mélanger dans une autre étape séparée un diluant édulcorant, un liant édulcorant supplémentaire et un arôme avec les produits des étapes (a) et (b) tout en ajoutant un lubrifiant ; (d) à comprimer éventuellement le mélange sur presse rotative.

L'invention se rapporte aussi à l'utilisation de la nouvelle association thérapeutique vitamino-calcique pour combattre l'ostéoporose.

L'invention est également relative aux caractéristiques ci-après :

— le rapport du calcium sous forme élémentaire à la vitamine D, exprimé en mg de Ca élément par UI de vitamine D, est compris entre 1 et 1,5, de préférence entre 1,2 et 1,3 ;

— le calcium sous forme élémentaire provient d'un sel de calcium choisi parmi le carbonate de calcium, le pidolate de calcium, le lactate de calcium, le citrate de calcium, le gluconate de calcium, le

chlorure de calcium, le glucoheptonate de calcium, le glycérophosphate de calcium et le phosphate de calcium ;

— la vitamine D est choisie parmi la vitamine D2 ou ergocalciférol, la vitamine D3 ou cholécalciférol ou un mélange de celles-ci ;

— le comprimé appartient au groupe comprenant les comprimés à croquer, les comprimés sécables, les comprimés à sucer, les comprimés à mâcher, les comprimés dispersibles et les comprimés pour suspension buvable ;

— l'un au moins dudit diluant édulcorant et dudit liant édulcorant est un agent de saveur propre à améliorer les caractéristiques gustatives de l'association, avantageusement un polyol, notamment choisi parmi le mannitol, le sorbitol, le xylitol et le maltitol ;

— le liant à sec et en milieu humide est choisi parmi une cellulose, la maltodextrine et la polyvinylpyrrolidone ;

— le lubrifiant est choisi parmi le stéarate de magnésium, l'acide stéarique, l'huile de ricin hydrogénée, l'huile de coton hydrogénée et le béhénate de glycérol ;

— l'association renferme en outre un agent aromatisant et/ou un acidifiant et/ou un édulcorant supplémentaire.choisi parmi le saccharinate de sodium, le cyclamate de sodium et l'aspartame ;

— l'association vitamino-calcique répond à la formule générale :

Calcium (carbonate de)	1 250 mg
(Quantité correspondant à calcium élément	500 mg)
Cholécalciférol	4 mg *
Xylitol	661 mg
Sorbitol	500 mg
Polyvinylpyrrolidone	45 mg
Arôme (citron, orange, etc.)	20 mg
Stéarate de magnésium	20 mg

(* Vitamine D3 dosée à 100 000 UI/g),

ladite formule correspondant à un comprimé terminé à 2 500 mg.

◊

Divers avantages et caractéristiques de la présente invention res-

sortiront d'un exemple de réalisation ci-après.

Dans cet exemple, l'association de l'invention se présente sous forme d'un comprimé à croquer de formule suivante (pour un comprimé terminé à 2500 mg) :

Calcium (carbonate de)	1 250 mg
(Quantité correspondant à calcium élément	500 mg)
Cholécalciférol	4 mg *
Xylitol	661 mg
Sorbitol	500 mg
Polyvinylpyrrolidone	45 mg
Arôme (citron, orange, etc.)	20 mg
Stéarate de magnésium	20 mg

(* Vitamine D3 dosée à 100 000 UI/g)

Le carbonate de calcium est du type SCORALITE 1B®, SCORA ; il s'agit d'une poudre blanche de granulométrie très fine d'un diamètre moyen de 12 micromètres environ, de densité élevée (d = 1,3 g/cm^3 environ) présentant un mauvais écoulement et une mauvaise aptitude à la compression.

La vitamine D est du cholécalciférol (type 100 CWS®, ROCHE) ; il s'agit d'une poudre granuleuse, de diamètre moyen de 200 micromètres environ, de couleur jaunâtre, dosée à 100 000 UI par gramme.

La présence de DL-α-tocophérol (environ 0,2 % m/m de vitamine E) lui confère une grande stabilité et empêche son oxydation.

Le diluant-édulcorant utilisé dans l'invention est de préférence du xylitol de type XYLITAB 300®, FINNSUGAR. Ce xylitol est un polyol de saveur sucrée (équivalente à celle du saccharose), procurant une agréable sensation de fraîcheur dans la bouche, il est acariogène et très peu calorique (2,4 Kcal/g contre 4 Kcal/g pour le saccharose). Cette sensation agréable permet une meilleure observance du traitement par le patient. Ce xylitol utilisé possède des propriétés de comprimabilité supérieures à celles du xylitol standard.

Ce composé se présente sous la forme d'une poudre granuleuse, cristalline blanche, d'un diamètre moyen de 250 micromètres.

Le liant-édulcorant utilisé dans la présente invention est en particulier du sorbitol (de type NEOSORB P 60 W®, ROQUETTE). Ce polyol se présente sous la forme d'une poudre granuleuse blanche, d'un diamètre moyen de 200 micromètres et possède d'excellentes propriétés liantes en compression. Le sorbitol est de saveur sucrée (70 % de celle du saccharose), acariogène et peu calorique (2,4 Kcal/g).

Le liant de la présente invention est, de préférence, de la polyvinylpyrrolidone (de type KOLLIDON K 30®, BASF) ; il se présente sous la forme d'une poudre blanchâtre granuleuse et possède de très grandes propriétés liantes en granulation humide. La valeur de la constante K caractérise les polyvinylpyrrolidones solubles et dépend de leur solubilité relative.

L'aromatisant est particulièrement un arôme citron (SBI) ; il se présente sous forme d'une poudre fine, jaunâtre, composée d'huiles essentielles atomisées sur de la maltodextrine. De nombreux essais réalisés durant la mise en oeuvre de la présente invention qui ont comparé différents arômes ont montré que l'arôme citron convenait parfaitement bien au masquage du goût crayeux du carbonate de calcium et qu'il s'associait agréablement à la sensation de fraîcheur apportée par le xylitol.

Le lubrifiant est généralement du stéarate de magnésium se présentant sous forme d'une poudre fine, blanchâtre, permettant d'éviter le phénomène de grippage au niveau des matrices des presses à comprimer quand l'association vitamino-calcique de la présente invention est sous forme de comprimés.

La quantité de calcium élémentaire par prise sera, de préférence, de 500 mg, ce qui correspond à 1250 mg de carbonate de calcium.

La quantité de cholécalciférol est de 4 mg par prise, ce qui correspond à 400 UI d'une vitamine D3 dosée à 100 000 UI/g. En pratique, la quantité de cholécalciférol par comprimé dépend du dosage de la matière première utilisée.

Ces doses correspondent notamment à la posologie optimale indiquée par les publications mentionnées plus haut, tant en valeur absolue (doses journalières de calcium et de vitamine D3, respectivement) que relative (ratio calcium/vitamine de l'ordre de 1,25 mg de Ca élé-

ment par UI de vitamine D).

Les nombreux essais des formules de cet exemple ont permis d'optimiser les quantités des différents excipients.

Pour obtenir un comprimé à croquer au goût le plus agréable, l'apport en liant à sec et en milieu humide combiné en quantité synergique avec au moins le diluant édulcorant, au moins le liant édulcorant et au moins le lubrifiant doit être important. Dans le cas d'un comprimé, celui-ci aura généralement une masse de 2500 mg.

Dans certaines formes de mise en oeuvre de la présente invention, on utilise une quantité de xylitol d'environ 661 mg, qui correspond à la quantité nécessaire à incorporer pour obtenir le meilleur masquage de goût du carbonate de calcium sans pour autant diminuer la comprimabilité du mélange, les propriétés du xylitol en compression étant moyennes.

Le sorbitol est utilisé à raison d'environ 500 mg car il s'agit de la quantité nécessaire à incorporer pour obtenir une parfaite reproductibilité de la fourchette de résistance à la rupture, paramètre critique dans le cas des comprimés à croquer. Une quantité supérieure, au détriment du xylitol, diminuerait les qualités gustatives du comprimé.

La polyvinylpyrrolidone est utilisée à raison d'environ 45 mg, lors de la granulation humide du carbonate de calcium, une partie (20 mg) est mélangée à sec avec le carbonate de calcium, la partie restante (25 mg) est utilisée en solution à 10 % dans de l'eau déminéralisée à froid. Une teneur en polyvinylpyrrolidone inférieure à 40 mg entraîne une trop grande friabilité des grains de carbonate de calcium. Une quantité plus importante n'apporte pas de réels bénéfices.

La quantité d'arôme citron est d'environ 20 mg, il s'agit de la quantité nécessaire pour aromatiser de façon satisfaisante le comprimé. Une faible variation de cette quantité (± 3 mg) ne modifie pratiquement pas le goût final.

La quantité de stéarate de magnésium est d'environ 20 mg. Il s'agit de la quantité nécessaire pour obtenir une lubrification satisfaisante lors de la compression. Une quantité plus faible, environ 15 mg, entraîne un phénomène de grippage, alors qu'une quantité supérieure, 25 mg tend à diminuer la dureté du comprimé et risque de modifier son goût.

Les caractéristiques physiques des éléments de l'association vitamino-calcique de la présente invention vont être indiquées ci-après.

Le carbonate de calcium a un écoulement nul et une densité apparente (g/cm^3) d'environ 1,28 à 1,35 et une humidité résiduelle en pour-cent de 0,1. La vitamine D3 cholécalciférol sous forme d'un concentrat de forme pulvérulente a un écoulement de 6 secondes pour 100 g de poudre, une densité apparente en g/cm^3 de 0,73, une humidité résiduelle en pour-cent de 6,4 et un dosage en UI/g de 100 000.

Le xylitol a un écoulement nul, une densité apparente en g/cm^3 d'environ 0,68-0,69, une humidité résiduelle en pour-cent de 0,2 à 0,3.

Le sorbitol a des écoulements dans la gamme de 4 à 5 secondes pour 100 g de poudre, une densité apparente en g/cm^3 de 0,71 à 0,73 et une humidité résiduelle en pour-cent de 0,5 à 0,8.

Les étapes de mise en oeuvre préférées du procédé d'obtention de l'association vitamino-calcique de la présente invention vont maintenant être exposées.

Une granulation humide du carbonate de calcium est tout d'abord effectuée.

Dans cette mise en oeuvre, le carbonate de calcium et la polyvinylpyrrolidone sont tamisés sur un tamiseur vibrant pourvu d'une grille d'ouverture de maille appropriée ; ces poudres sont introduites dans un mélangeur et mélangées peu de temps à une vitesse appropriée. De la solution de polyvinylpyrrolidone est ajoutée par étapes successives. Une granulation est effectuée jusqu'à l'obtention d'une masse humide, permettant une étape de précalibrage suivante.

Une précalibration est effectuée sur un granulateur muni d'une grille d'ouverture de maille appropriée.

Le produit résultant est séché sur un lit d'air fluidisé et laissé à refroidir.

La perte de masse à la dessiccation est déterminée et une calibration sur une grille d'ouverture de maille appropriée est effectuée.

Parallèlement, la vitamine D3 est prémélangée et, après un tamisage, elle est mélangée avec du sorbitol dans un mélangeur pendant une durée appropriée et à une vitesse de rotation convenable.

On réalise ensuite le mélange avec les autres constituants en tami-

sant du xylitol, du sorbitol et l'arôme sur un tamis vibrant équipé d'une grille à ouverture de mailles appropriée. On mélange ces trois constituants avec le prémélange de vitamine D3-sorbitol dans un mélangeur à une vitesse appropriée. On introduit ensuite le carbonate de calcium granulé et on le mélange pendant la durée requise à la vitesse appropriée.

Le stéarate de magnésium est tamisé sur un tamis vibrant muni d'une grille d'ouverture de maille appropriée puis l'ensemble est mélangé dans un mélangeur.

L'ensemble ci-dessus peut être ensuite comprimé sur une presse à comprimer en contrôlant régulièrement l'uniformité de la masse et la résistance à la rupture. Les durées de mélange, les vitesses de rotation et les dimensions des tamis sont classiques et sont bien connues de l'homme du métier.

Ainsi, la présente invention permet d'obtenir une association vitamino-calcique contenant 500 mg de calcium élémentaire et 4 mg de vitamine D3 par prise, association qui est notamment sous la forme d'un comprimé à croquer qui est d'un goût agréable et d'une dureté adaptée aux patients.

Plus particulièrement, à titre d'exemple non limitatif, les doses qui seront généralement utilisées se situeront dans les gammes suivantes : calcium sous forme élémentaire, environ 500 mg à environ 1500 mg ; vitamine D ou mélange de vitamines D, environ 3,5 mg à environ 12 mg. Une telle association vitamino-calcique, notamment sous forme de comprimés, ne contient ni sucre ni sodium.

Cependant, d'autres formes galéniques sont possibles.

On peut ainsi réaliser un comprimé sécable (à avaler) de formule suivante, pour un comprimé de 1,60 g :

Carbonate de calcium	1,250 g
Vitamine D3	0,004 g
Cellulose microcristalline	0,236 g
Polyvinylpyrrolidone	0,040 g
Stéarate de magnésium	0,020 g

De façon générale, pour la mise en oeuvre de comprimés du type à croquer ou à sucer on utilisera du carbonate de calcium. D'autres sels tels que le triphosphate de calcium peuvent être utilisés, mais leur absorption par l'organisme est moindre, ce qui conduit à adapter les quantités en conséquence (pour une même quantité de calcium élémentaire absorbé, il faut environ 1,2 g de triphosphate de calcium pour 1 g de carbonate de calcium).

REVENDICATIONS

1. Association thérapeutique vitamino-calcique sous forme galénique unitaire de comprimés, comprenant comme principes actifs associés du calcium sous forme élémentaire et au moins une vitamine D, caractérisée en ce qu'elle renferme, en outre, au moins un liant à sec et en milieu humide combiné en quantité synergique avec au moins un diluant, au moins un liant et au moins un lubrifiant, l'un au moins dudit diluant et dudit liant étant un édulcorant.

2. Association selon la revendication 1, où le rapport du calcium sous forme élémentaire à la vitamine D, exprimé en mg de Ca élément par UI de vitamine D, est compris entre 1 et 1,5.

3. Association selon la revendication 2, où le rapport du calcium sous forme élémentaire à la vitamine D, exprimé en mg de Ca élément par UI de vitamine D, est compris entre 1,2 et 1,3.

4. Association selon la revendication 1, où le calcium sous forme élémentaire provient d'un sel de calcium choisi parmi le carbonate de calcium, le pidolate de calcium, le lactate de calcium, le citrate de calcium, le gluconate de calcium, le chlorure de calcium, le glucoheptonate de calcium, le glycérophosphate de calcium et le phosphate de calcium.

5. Association selon la revendication 1, où la vitamine D est choisie parmi la vitamine D2 ou ergocalciférol, la vitamine D3 ou cholécalciférol ou un mélange de celles-ci.

6. Association selon la revendication 1, où le comprimé appartient au groupe comprenant les comprimés à croquer, les comprimés sécables, les comprimés à sucer, les comprimés à mâcher, les comprimés dispersibles et les comprimés pour suspension buvable.

7. Association selon la revendication 1, où l'un au moins dudit diluant édulcorant et dudit liant édulcorant est un agent de saveur pro-

pre à améliorer les caractéristiques gustatives de l'association.

8. Association selon la revendication 7, où l'un au moins dudit diluant édulcorant et dudit liant édulcorant est un polyol.

9. Association selon la revendication 8, où le polyol est choisi parmi le mannitol, le sorbitol, le xylitol et le maltitol.

10. Association selon la revendication 1, où le liant à sec et en milieu humide est choisi parmi une cellulose, la maltodextrine et la polyvinylpyrrolidone.

11. Association selon la revendication 1, où le lubrifiant est choisi parmi le stéarate de magnésium, l'acide stéarique, l'huile de ricin hydrogénée, l'huile de coton hydrogénée et le béhénate de glycérol.

12. Association selon la revendication 1, renfermant en outre un agent aromatisant.

13. Association selon la revendication 1, renfermant en outre un acidifiant.

14. Association selon la revendication 1, renfermant en outre un édulcorant supplémentaire choisi parmi le saccharinate de sodium, le cyclamate de sodium et l'aspartame.

15. Association selon la revendication 3, de formule générale :

Calcium (carbonate de)	1 250 mg
(Quantité correspondant à calcium élément	500 mg)
Cholécalciférol	4 mg *
Xylitol	661 mg
Sorbitol	500 mg
Polyvinylpyrrolidone	45 mg
Arôme (citron, orange, etc.)	20 mg
Stéarate de magnésium	20 mg

(* Vitamine D3 dosée à 100 000 UI/g),
ladite formule correspondant à un comprimé terminé à 2 500 mg.

16. Procédé d'obtention d'une association thérapeutique vitamino-calcique sous forme galénique unitaire de comprimés comprenant comme principes actifs associés du calcium sous forme élémentaire et au moins une vitamine D, caractérisé en ce qu'il consiste :

(a) à granuler le calcium sous forme élémentaire avec un liant à sec et en milieu humide ;

(b) à prémélanger la vitamine D avec un liant édulcorant dans une étape séparée ;

(c) à mélanger dans une autre étape séparée un diluant édulcorant, un liant édulcorant supplémentaire et un arôme avec les produits des étapes (a) et (b) tout en ajoutant un lubrifiant ;

(d) à comprimer éventuellement le mélange sur presse rotative.

17. L'utilisation de l'association thérapeutique vitamino-calcique de l'une des revendications 1 à 15 pour combattre l'ostéoporose.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FR 95/01053

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 413 828 (TEIJIN LIMITED) 27 February 1991 see claims 1-7 see page 2, line 11 - line 19 see page 5, line 5 - line 29	1,4-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 1995	17. 11. 95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Ventura Amat, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[illegible]nal Application No
PCT/FR 95/01053

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-413828	27-02-91	JP-A-	2229115	11-09-90
		CA-A-	2027592	02-09-90
		WO-A-	9009796	07-09-90
		KR-B-	9310621	02-11-93
		US-A-	5158944	27-10-92

RAPPORT DE RECHERCHE INTERNATIONALE

De le internationale No
PCT/FR 95/01053

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 6 A61K9/00

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 6 A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si cela est réalisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
X	EP,A,0 413 828 (TEIJIN LIMITED) 27 Février 1991 voir revendications 1-7 voir page 2, ligne 11 - ligne 19 voir page 5, ligne 5 - ligne 29	1,4-17

☐ Voir la suite du cadre C pour la fin de la liste des documents

☒ Les documents de familles de brevets sont indiqués en annexe

* Catégories spéciales de documents cités:

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(54) Title: PROCESS FOR PREPARING ORAL CALCIUM COMPOSITIONS

(57) Abstract

The invention provides a process for the preparation of an orally administrable calcium composition, said process comprising the steps of: (i) obtaining a physiologically tolerable particulate calcium compound having a mean particle size in the range 3 to 40μm, having a crystalline structure and having a surface area of 0.1 to 1.2 m^2/g; (ii) mixing said calcium compound with a water–soluble diluent and an aqueous solution of a water soluble binder in a fluid bed granulation apparatus and drying the resulting mixture to produce a first granulate; (iii) optionally mixing said first granulate with one or more further components to produce a second granulate; and (iv) optionally compressing said first or second granulate to form tablets.

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Process for preparing oral calcium compositions

This invention relates to a process for the manufacture of an orally administrable pharmaceutical composition containing a physiologically tolerable calcium compound, in particular a composition in tablet form.

Calcium carbonate tablets are used as a source of calcium, especially for patients suffering from or at risk of osteoporosis. Moreover calcium carbonate is used as an acid neutralizing agent in antacid tablets.

Calcium carbonate is used in such tablets since the calcium content of calcium carbonate is high, the calcium is presented in a form which can be taken up from the gastrointestinal tract, calcium carbonate is effective at neutralizing gastric acids, and calcium carbonate is a physiologically acceptable calcium compound.

In such tablets, various binders, sweeteners and flavors are used in order to produce a tablet which is readily acceptable to the patient. Indeed many producers have sought to achieve improved patient acceptability by formulating the tablets with such excipients in a "chewable" form. As a result, and since the daily recommended dosage is generally about 1000 mg calcium, the commercially available calcium tablets which commonly contain 500 mg calcium are relatively bulky.

Examples of chewable calcium carbonate tablets are described in WO 96/09036 (Laboratoire Innothera) and in US-A-4446135 (Sterling Drug). The chewable calcium carbonate tablets described in these two patent publications have a calcium carbonate content of about 50% or less by weight and for a 500 mg calcium dosage are therefore undesirably large.

The present invention is directed to a process by which this undesired bulk may be reduced, and in particular to a process by which a chewable calcium tablet may be produced with a calcium compound content in excess of 60% by weight.

Thus viewed from one aspect the present invention provides a process for the preparation of an orally administrable calcium composition, said process comprising the steps of:

(i) obtaining a physiologically tolerable particulate calcium compound having a mean particle size in the range 3 to 40μm, having a crystalline structure and having a specific surface area of 0.1 to 1.2 m^2/g, preferably 0.2 to 0.9 m^2/g, especially 0.3 to 0.8 m^2/g;

(ii) mixing said calcium compound with a water-soluble diluent and an aqueous solution of a water soluble binder in a fluid bed granulation apparatus and drying the resulting mixture to produce a first granulate;

(iii) optionally mixing said first granulate with one or more further components to produce a second granulate, preferably a granulate having a content of said calcium compound of at least 60% by weight; and

(iv) optionally compressing said first or second granulate to form tablets.

The physical characteristics of the calcium compound used in the process of the invention are important in order that the fluid bed granulation stage should produce a first granulate having the desired characteristics. The calcium compound should be crystalline and have a mean particle size of 3 to 40μm, preferably 5 to 30μm. Preferably it should have a bulk density in the range of 0.2 to 1.5g/mL, more preferably 0.3 to 1.4g/mL, especially 0.4 to 1.3g/mL. The calcium compound is preferably an acid soluble compound, e.g. a compound poorly soluble or insoluble in water at pH7 but soluble in water at gastric pH values.

The upper particle size limit of 40μm is important in order to avoid a gritty mouthfeel in the final product. The lower particle size limit of 3μm is also important in order to avoid a feeling of stickiness on the teeth during chewing.

Crystallinity, in particular the possession of relatively smooth crystal surfaces and low specific surface area, is important for the achievement of effective and rapid wetting and granulation in the fluid granulation step of the process of the invention.

Specific surface area may be determined using apparatus such as the Carlo Erba Sorptomatic 1900.

The calcium compound may, for example, be selected from calcium carbonate, calcium lactate, calcium gluconate, calcium citrate, calcium glycerophosphate, calcium phosphate, calcium hydrogen phosphate (e.g. in tribasic, dibasic or monobasic forms, i.e. $Ca_3(PO_4)_2$, $CaHPO_4.2H_2O$ and $Ca(HPO_4)_2.H_2O$), calcium glucuronate, calcium aspartate, calcium glucoheptonate and mixtures of two or more thereof. However, calcium carbonate, in particular in calcite form, is preferred due to its high calcium content, its ready availability, its cost, its well-documented absorption characteristics in humans, and its performance in the fluid granulation step of the process of the invention.

Especially, preferably calcium carbonate having individual or primary and cubic or pseudo-cubic shaped calcite crystals with smooth or even surfaces are used. Desirably such crystals are also transparent. Where the end product is for use as a medicine, it is also preferred that the calcium carbonate be a material precipitated according to Ph. Eur.

Examples of appropriate commercially available calcium carbonate include Merck 2064 (available from Merck, Darmstadt, Germany), Scoralite 1A and Scoralite 1B (available from Scora Watrigant SA, France), Super-Purity $CaCO_3$ and Medicinal Heavy $CaCO_3$ (available from

Shanghai Da Yu Biochemistry Co. Ltd., China), and Pharmacarb LL (available from Crompton & Knowles, Vineland, USA). Scoralite 1B and Scoralite 1A + 1B are particularly preferred. Merck 2064 has a mean particle size of 10 to 30μm, an apparent bulk density of 0.4 to 0.7 g/mL, and a specific surface area of 0.3 m^2/g; Scoralite 1A has a mean particle size of 5 to 20μm, an apparent bulk density of 0.7 to 1.0g/mL and a specific surface area of 0.6 m^2/g; Scoralite 1A + 1B has a mean particle size of 7 to 25 μm, an apparent bulk density of 0.7 to 1.2 g/mL and a specific surface area of 0.35 to 0.8 m^2/g; Scoralite 1B has a mean particle size of 10 to 30μm, an apparent bulk density of 0.9 to 1.3 g/mL and a specific surface area of 0.4 to 0.6 m^2/g; Medicinal Heavy $CaCO_3$ has a mean particle size of 5 to 30 μm, an apparent bulk density of 0.9 to 1.3 g/mL and a specific surface area of 0.8 m^2/g; Super-Purity $CaCO_3$ has a mean particle size of 10 to 30 μm, an apparent bulk density of 0.9 to 1.2 g/mL and a specific surface area of 0.6 m^2/g; and Pharmacarb LL has a mean particle size of 5 to 30 μm, an apparent bulk density of 0.8 to 1.2 g/mL and a specific surface area of 0.7 m^2/g. The Pharmacarb LL calcium carbonate however is not apparently a material precipitated in accordance with Ph. Eur. and thus is more preferred for production of end products which are for use as dietary supplements or food products than those which are for use as pharmaceuticals.

The calcium compound or mixture of calcium compound preferably makes up 60 to 95% by weight of the second granulate, and preferably provides a calcium content of 15 to 40%, more especially 20 to 35%, and still more especially 25 to 30% by weight in the second granulate.

The calcium compound or mixture of compounds preferably makes up 60.5 to 96%, more preferably 66 to 91% still more preferably 68 to 80% and most preferably 72 to 76% by weight of the first granulate.

The water-soluble diluent used in step (ii) of the

process of the invention is preferably a sweetener or a mixture of sweeteners, e.g. a polyol or a polysaccharide, more preferably a non-cariogenic sweetener. Examples of suitable diluents include sorbitol, xylitol, isomalt and mannitol, which are non-cariogenic. Neosorb P100T sorbitol, xylitol CM50 and isomalt PF are available commercially from Roquette Freres, Xyrofin and Palatinit respectively. Further examples of suitable saccharide-based diluents include sucrose, fructose and the maltodextrins (e.g. Lycatab DSH available from Roquette Freres). Especially preferred as diluents are the non-cariogenic oligosaccharides such as inulin and oligofructose. Inulin may be obtained by extraction from chickory root and is available under the trade name Raftiline from Orafti SA, Tieren, Belgium. Oligofructose is obtained by partial hydrolysis of inulin and is available from Orafti SA under the trade name Raftilose and from Beghin-Meiji Industries, Neuilly-sur-Seine, France under the trade name Actilight.

The diluent preferably makes up the major proportion, e.g. by 70 to 96%, more preferably 80 to 95%, still more preferably 85 to 94%, most preferably 90 to 92% of the total weight of diluent and binder in the first granulate.

The calcium compound and diluent (which, especially in the case of inulin, may be the same material as is used as the binder) are preferably blended before addition of the aqueous binder. The blending may conveniently be performed as a dry blending, for example using a blender with a rotating mixer arm, e.g. a blade. This ensures that any lumps are removed and achieves an intimate mixing of the calcium compound and the diluent. By way of example, a high speed mixer (e.g. Fielder PMA 25/2G) may be used operating at maximum speed for both the impeller and knife for two minutes; however any mill may be used to break up lumps in the mixture and indeed

the calcium compound and the diluent may be treated in this way separately to remove lumps before they are blended.

The water-soluble binder used in step (ii) of the process of the invention may be selected from known water-soluble pharmaceutical binders, e.g. it may be a soluble cellulose or polysaccharide or a polyvinylpyrrolidone or a mixture thereof. Preferably the binder is a polyvinylpyrrolidone, e.g. Kollidon K30, Kollidon 90F or Kollidon VA64 which are available commercially from BASF. Inulin and maltodextrin may also be used as binders.

The binder is preferably used in aqueous solution at a concentration of 10 to 35% by weight, more especially 15 to 35%, preferably 25 to 30%, and particularly 27 to 29% by weight.

The fluid granulation step, step (ii) of the process of the invention, may be effected in any fluid granulation apparatus, e.g. a Glatt GPCG 3 fluid bed available from Glatt GmbH. The procedure preferably involves spraying the aqueous binder mixture onto the fluidized diluent/calcium compound mixture. Fluidization may be achieved by gas flow through the mixture or alternatively mechanically, e.g. by the use of counter-rotating, interlocking paddles with horizontal rotational axes. The liquid sprayed is preferably at or near ambient temperature (e.g. 15 to 35°C, preferably 20 to 30°C, more preferably about 25°C) and the particulate onto which it is sprayed is again preferably at or near ambient temperature (e.g. 15 to 35°C, preferably 20 to 30°C, more preferably about 25°C). The gas pressure of the spray chamber is conveniently ambient (e.g. 1 atmosphere). The spray rate may be adjusted, according to batch size and component identities and concentrations, to optimize the mean particle size of the first granulate. However, for a 3kg solids batch, a spray rate of 30 to 50g/min may be

appropriate and a spray rate of about 40g/min is particularly preferred.

The granulate may be dried in a separate drier but preferably is dried in place in the fluidized bed mixer, e.g. using a heated gas (e.g. air) flow through the granulate. This can be effected while spraying of the binder solution is taking place or after spraying of the binder solution has been completed. Clearly if drying is effected during spraying it should be completed after spraying has stopped. Preferably a drying gas temperature of 60 to 90°C, more especially 65 to 75°C, in particular about 70°C is used. Particularly preferably drying is effected such that the granulate temperature reaches 40 to 50°C, especially about 43 to 45°C.

In this way a first granulate having a low water content, e.g. 1 to 5% by weight, preferably about 3%, may be produced and subsequently dried to a moisture content of about 0.1 to 0.5%, preferably 0.2% by weight, within an overall granulation and drying period of 15 to 45 mins, preferably 20 to 30 mins.

The first granulate preferably has a particle size distribution (as determined by Malvern particle size analysis) as follows:

D (v, 0.1) = 15-21 μm

D (v, 0.5) = 70-120 μm

D (v, 0.9) = 190-330 μm

Where the first granulate is to be mixed with further components before tabletting, such further components will typically be one or more of the following: further active agents, e.g. vitamins, in particularly vitamin D, especially vitamin D_3; effervescing agents; diluents; sweeteners; flavors; acidulants; and lubricants, e.g. hydrogenated fatty acids, polyethyleneglycol, sodium stearyl fumarate, stearic acid and salts thereof, for example magnesium stearate. When a further active agent is added, this should be at a therapeutically effective dosage. When

vitamin D is added, e.g. to produce a product suitable for treatment or prophylaxis of osteoporosis, this preferably is at a calcium to vitamin D ratio of 100 mg Ca: 30 to 150 IU Vitamin D, especially 100:35 to 100 IU, more especially 100:40 to 90 IU. Preferably the second granulate should be such as to be tablettable to produce tablets containing 500mg Ca and 200 to 250 IU or 400 to 450 IU vitamin D_3.

Where vitamin D is used, this may conveniently be vitamin D_2 (ergocalciferol) or more preferably vitamin D_3 (cholecalciferol). Dose units of the second granulate, e.g. tablets formed therefrom, preferably contain 250 to 1500mg Ca and 5 to 30μg vitamin D.

Vitamin D_3 is commercially available from Roche in a granular form which consists of vitamin D_3 in edible fats finely dispersed in a starch coated matrix of gelatin and sucrose with D,L-α-tocopherol added as an antioxidant. However, other dry powder or granulate forms of vitamin D may also be used.

A chewable tablet containing 500 mg calcium and 5 μg vitamin D_3 only contains 2.2 mg of the commercial quality of vitamin D_3 from Roche (100 CWS). This constitutes only 0.13% of the total weight of the tablet and one may thus anticipate problems with the homogeneity of vitamin D_3 in the tablet. A Malvern particle size analysis of the 100 CWS quality typically gives the following results for the particle size distribution: D(v, 0.1)=180-250 μm, D(v, 0.5)=240-300 μm and D(v, 0.9)=320-400 μm. It has been found desirable to sieve the vitamin D_3 on 60 mesh (250 μm) with a Russell vibrating sieve. This procedure will increase the number of vitamin D_3 particles per tablet and thus facilitate a more even and uniform distribution. In addition to this the sieving procedure will also eliminate all the coarse particles in the vitamin D_3 which also contribute to an inhomogeneous distribution.

Twenty consecutive batches of a chewable tablet

containing 500 mg calcium and 5 μg vitamin D_3 have been produced which have utilized a sieved (< 60 mesh) vitamin D_3 with a mean particle size in the region of 203-217 μm. All twenty batches comply with the requirements set in the European Pharmacopeia with respect to the uniformity of content of vitamin D_3 in the tablet.

Other active ingredients can be included in the compositions produced according to the invention. Examples include isoflavones, vitamin K, vitamin C, vitamin B_6 and oligosaccharides such as inulin and oligofructose. Isoflavones exhibit a weak oestrogenic effect and can thus increase bone density in post-menopausal women. Isoflavones are available under the trade name Novasoy 400 from ADM Nutraceutical, Illinois, USA. Novasoy 400 contains 40% isoflavones and will typically be used in an amount sufficient to provide 25 to 100 mg isoflavone/dosage. Isoflavones may be included in the second granulate; however as Novasoy 400 is a relatively cohesive powder it is preferred that it be included in the first granulate in order to ensure that it is uniformly distributed. Vitamin K (more especially vitamin K_1) may improve biochemical markers of bone formation and bone density and low concentrations of vitamin K_1 have been associated with low bone mineral density and bone fractures. Vitamin K_1 is available from Roche as Dry Vitamin K_1, 5% SD, a dry substance containing 5% vitamin K_1. Typically vitamin K_1 will be used in a quantity sufficient to provide 0.05 to 5 mg vitamin K_1/dosage. Vitamin C and vitamin B_6 (available from Roche, Takeda and BASF amongst others) function as co-factors in the formation of collagen, the main component of the organic matrix of bone. Vitamin C and vitamin B_6 will typically be used in quantities sufficient to provide 60 to 200 mg vitamin C/dosage and 1.6 to 4.8 mg vitamin B_6/dosage respectively. Oligosaccharides have been shown to facilitate and

increase calcium absorption and may typically be used in quantities sufficient to provide 0.3 to 5 g oligosaccharide/dosage. In general it is desirable that a total of at least 5g oligosaccharide is administered daily to facilitate calcium uptake and to obtain a pre-biotic effect.

Where an active component is used which forms a minor part of the overall granulate, e.g. vitamin D, it is general preferred to produce a premix of such a component and the first granulate before mixing the premix and the remaining required quantity of the first granulate. This ensures uniform distribution of the minor component in the second granulate.

The second granulate also preferably contains a flavor, e.g. a fruit flavor, in particular a lemon or orange flavor, in order to mask the chalky taste of calcium carbonate. The flavor may, for example, be a lemon or orange oil dispersed in a hydrogenated glucose syrup material or, alternatively, it may be any other stable flavor, e.g. one of the Durarome flavors available from Firmenich.

Extra sweeteners, e.g. artificial sweeteners such as aspartame, acesulfame K, saccharin, sodium saccharin, neohesperidine hydrochloride, taumatin and sodium cyclamate may be used to enhance the sweetness of the granulate.

Acidulants, e.g. anhydrous citric acid, malic acid, or any other organic acid with suitable organoleptic properties may be used in order to complement and enhance the flavour and sweetness of the dosage form.

Such extra components may be mixed in during the fluid granulation step of the process of the invention, but preferably they are mixed in with the first granulate in a separate dry mixing step, optionally after a sieving step to ensure homogeneous mixing.

When the granulate is to be tabletted, it preferably includes a lubricant, e.g. magnesium

stearate, stearic acid, hydrogenated fatty acids, sodium stearyl fumarate, PEG 6000 or PEG 8000. Magnesium stearate is generally preferred. Such a lubricant will generally make up 0.3 to 1.5%, particularly 0.35 to 1.0% by weight of the composition to be tabletted. The lubricant is preferably added in a final mixing step and mixed in for a brief time to prevent overmixing and subsequent lack of cohesion in the tabletted product.

Where the granulate is to be tabletted, this can be effected on conventional tablet presses. Preferably the tablet so produced will have a total weight of 500 to 3800mg, e.g. 500 to 3000 mg, more especially 1000 to 2500mg, most preferably 1500 to 2000mg. If desired however, the granulate (either the first granulate or the second granulate) may be used for other administration forms, e.g. powders, capsules, lozenges, coated tablets, etc. In general dose units (e.g. tablets or sachet contents) will contain 100 to 1000 mg Ca, especially 250 to 750 mg Ca, most preferably 450 to 550 mg Ca. The granulate is itself novel and forms a further aspect of the invention. Viewed from this aspect, the invention provides a granulate, preferably a tablettable granulate, comprising a fluid bed granulation granulate product of a physiologically tolerable calcium compound, a water-soluble binder and a water-soluble diluent, said calcium compound having a mean particle size in the range 3 to 40μm, having a crystalline structure and having a surface area of 0.1 to 1.2 m^2/g.

The present invention makes it possible to reduce the amount of soluble diluent and binder in a chewable calcium tablet while sustaining the desirable chewability by the production of a highly porous granulate by fluid bed granulation using a calcium compound with a relatively high degree of crystallinity and with smooth faces to the crystals. This high degree of porosity, desirably 20 to 30%, results in the final

chewable tablet having improved sensoric properties despite having a high calcium content. Such properties include improved dispersion in water and reduced stickiness during mastication.

The porosity of the granulate or tablet may be determined using mercury intrusion porosimetry (e.g. using a Carlo Erba Porosimeter 2000), and by helium adsorption, e.g. using an AccuPyc 1330 pycnometer to measure true density and a Geopyc 1360 envelope measuring apparatus. AccuPyc 1330 and Geopyc 1360 apparatus are available from Micrometrics. Mercury intrusion porosimetry is the more suitable of the two techniques for measuring the porosity of a granulate while both techniques can be used for measuring the porosity of a tablet.

Viewed from a further aspect the invention provides a tablet (e.g. a lozenge, chewable tablet or a effervescent tablet) comprising a compressed granulate according to the invention and containing: calcium carbonate; vitamin D_3; a lubricant; citric acid; and an oligosaccharide; and, optionally but preferably, polyvinylpyrrolidone.

The invention will now be described further with reference to the following non-limiting Examples and the accompanying drawings in which Figures 1 to 6 are scanning electron micrographs of six different grades of calcium carbonate and Figures 7A, 7B, 8A and 8B are scanning electron micrographs of granulates prepared according to the invention at lower (Figs. 7A and 8A) and higher (Figs. 7B and 8B) magnification:

EXAMPLE 1

Preparation of First Granulate

A binder solution is prepared containing 27.7% by weight of polyvinylpyrrolidone (Kollidon K30) in purified water. This is temperature-controlled at 20°C

or more preferably 25°C before spraying.

A batch of 74.5 parts by weight calcium carbonate (Scoralite 1B) and 23.3 parts by weight sorbitol (Neosorb P100T) is blended for two minutes using a high speed mixer (Fielder PMA 25/2G) set at maximum mixing speed. 3.0kg of this blend are then placed at 23-26°C in the mixer chamber of a Glatt GPCG3 fluid bed mixer.

The polyvinylpyrrolidone solution is then sprayed onto the fluidized blend at a rate of 40g/min until a total of 280g of liquid has been added. Spraying is effected into air at an inlet temperature of 45°C and at ambient pressure.

Air at 70°C is then passed through the sprayed granulate until it is dry (about 0.2% by weight residual moisture content). At this stage, the granulate temperature is about 44°C. The total duration of the spraying and drying stage is about 25 minutes.

At the end of the drying stage the first granulate has the following properties:

mean particle size and distribution D(v, 0.1) = 16 μm, D(v, 0.5) = 100 μm, and D(v, 0.9) = 284μm

Bulk density: 0.73g/mL

Porosity: 20-30%

Flowability (Carrs index %) : 13

The mean particle size analysis is performed on a Malvern Mastersizer S long bench apparatus D(v,0.1), D(v,0.5), and D(v,0.9) give the particle sizes for which 10%, 50% and 90% of the particles by volume have sizes below the given values.

EXAMPLE 2

Preparation and Tabletting of Second Granulate

4.4 parts by weight of sieved (< 60 mesh) Vitamin D_3 from Roche and 32 parts by weight of the first granulate are dry mixed in a twin cone convection blender to form a pre-mix.

The pre-mix, the first granulate, lemon flavour granulate and aspartame are then dry mixed in a conical screw mixer to produce a granulate which is then mixed for 9 minutes. Magnesium stearate is added and mixed for an additional 3 minutes to produce a second granulate comprising:

Calcium carbonate	1250 parts by weight
Sorbitol	390 parts by weight
Polyvinylpyrrolidone	36.4 parts by weight
Vitamin D_3 100 000 IU/g (100CWS from Roche)	4.4 parts by weight
Lemon flavour (in dehydrated glucose syrup)	50.7 parts by weight
Aspartame	1 part by weight
Magnesium stearate	6 part by weight

This mixture is then tabletted to produce biconvex tablets of 16mm diameter containing 1250 mg calcium carbonate.

The characteristics of the tablets are as follows:

Breaking strength: The chewable tablet has a normal biconvex shape and a diameter of 16 mm. The tablet initially has a breaking strength of 6 to 7.5 kp which can increase to approximately 8 to 9 kp after 24 hour storage. This breaking strength gives a satisfactory chewability and at the same time resistance towards handling and packaging into tablet bottles.

The initial breaking strength values may however vary between 4.5 to 8.0 kp according to the size of the tablet (12-21 mm).

Friability: A breaking strength of 6 to 7.5 kp for a chewable tablet with a diameter of 16mm results in friability values of less than 1%. This low value for the friability ensures sufficient firmness with respect to handling and packaging.

Disintegration: A characteristic feature of this chewable tablet formulation is the very fast disintegrating time.

The disintegration time is typically between 3 and 6 min. It is also a characteristic feature of the tablet that it disintegrates into the primary crystals of calcium carbonate which ensures a rapid exposure of calcium carbonate for dissolution.

This is important for the in vivo dissolution of calcium carbonate in the acidic gastric medium in the stomach and the subsequent absorption of calcium in the gastrointestinal tract.

Porosity: The tablet has a characteristic porosity of 25-30%. The porosity is determined by both mercury intrusion porosimetry and helium adsorption as described above. Both techniques gave porosity values in the range 25-30% for the tablet.

Dissolution: The dissolution rate is typically quick with 90% elemental calcium being dissolved within 10 min in 900 ml of 0.1 N HCl at 37°C (Ph. Eur., rotating paddle at 50 RPM).

EXAMPLE 3

Lozenge to be sucked

Using a process analogous to that of Examples 1 and 2 lozenges are prepared with the following composition:

Calcium granulate:	
Calcium carbonate (Scoralite 1B):	1250 mg
Xylitol (CM50):	390 mg
Polyvinylpyrrolidone (Kollidon K 30):	36.40 mg
Vitamin D_3 100 000 IU/g (100 CWS from Roche):	4.4 mg
Lemon flavor:	50.7 mg
Anhydrous citric acid:	8.0 mg
Aspartame:	1.0 mg
Magnesium stearate:	6.0 mg
Sum tablet weight:	1747 mg

EXAMPLE 4

Sachet product to be dispersed in a glass of water

Using a process analogous to that of Examples 1 and 2 but with sorbitol replaced by anhydrous citric acid, sachets are prepared with the following granulate contents:

Calcium granulate:	
Calcium carbonate (Scoralite 1A):	1250 mg
Citric acid, anhydrous (powder quality)	2150 mg
Polyvinylpyrrolidone (Kollidon VA 64 or 90F):	36.60 mg
Vitamin D_3 100 000 IU/g (100 CWS from Roche):	4.4 mg
Lemon flavor:	300 mg
Aspartame:	15.0 mg
Acesulfam K:	14.0 mg
Sum sachet contents weight:	3770 mg

EXAMPLE 5

Granulate to be dispensed from a granulate dispensing unit

This product may be used as a food additive or as a functional food where the consumer takes a dosage equivalent to 500-1000 mg of elemental calcium and uses this as a supplement in daily food products, such as for example breakfast cereals and fruit juices. The granulate is produced by a process analogous to that of Examples 1 and 2 with the following composition:

Calcium granulate:	
Calcium carbonate (Scoralite 1A+1B):	1250 mg
Xylitol (CM 50):	390 mg
Polyvinylpyrrolidone (Kollidon VA 64):	36 mg
Granulate weight per 500 mg Ca^{2+}:	1676 mg

In this Example, polyvinylpyrrolidone may be replaced by inulin (e.g. Raftiline ST), 36.60 mg. Additional inulin or oligofructose may be added to bring the total oligosaccharide content to 1 to 5 g per dosage.

EXAMPLE 6

Effervescent tablet to be dispersed in a glass of water

Using a process analogous to that of Examples 1 and 2, effervescent tablets are prepared with the following composition:

Calcium granulate:	
Calcium carbonate (Scoralite 1A+1B):	1250 mg
Citric acid, anhydrous (powder quality)	2150 mg
Polyvinylpyrrolidone (Kollidon VA 64 or 90F):	36.60 mg
Vitamin D_3 100 000 IU/g (100 CWS from Roche):	4.4 mg
Lemon flavor:	300 mg
Aspartame:	15.0 mg
Acesulfam K:	15.0 mg
Sodium stearate fumarate:	19.0 mg
Sum tablet weight:	3790 mg

In this Example, aspartame and acesulfam K may be partially or totally replaced by inulin or oligofructose with these providing 1 to 4 oligosaccharide per tablet.

EXAMPLE 7

Calcium carbonate grades

Samples of Scoralite 1B, Scoralite 1A, Super Purity $CaCO_3$, Medicinal Heavy $CaCO_3$, Pharmacarb LL and Merck 2064 were investigated using a scanning electron

microscope (SEM). SEM pictures of these grades of calcium carbonate are presented in Figures 1 to 6 respectively of the accompanying drawings.

Granulates made analogously to Example 1 using Scoralite 1B and Super Purity $CaCO_3$ were also investigated by SEM and SEM pictures of these granulates at lower (A) and higher (B) magnifications are presented in Figures 7 and 8 of the accompanying drawings. The pictures of the two granulates clearly show their high degree of porosity, a property which is important for the fast disintegration/dissolution of tablets made therefrom. Moreover, this high degree of porosity is important for the sensory properties such as chewability and avoidance of sticking to the teeth during mastication.

EXAMPLES 8 TO 12

Analogously to Examples 1 and 2, chewable tablets and lozenges are prepared with the compositions set out in Table 1 below. The difference between a chewable tablet and a lozenge is simply in crushing strength or hardness, the lozenge being more forceably compressed so that it can be sucked and will last longer in the mouth.

The concentration of the binder in the aqueous granulation liquid and the granulation spray rate are adjusted in Examples 9 to 12 as follows:

Example 9: 20% maltodextrin solution, spray rate 31 g/min

Example 10: 15% inulin solution, spray rate 28 g/min.

Example 11: 15% inulin solution, spray rate 31 g/min.

Example 12: 28% PVP solution, spray rate 31 g/min.

Example Number	8	9	10	11	12
Ingredients in calcium granulate					
$CaCO_3$[1]	1250 mg	1250 mg	1250 mg	1250 mg	1250 mg
Isoflavone extract[2]	-	-	-	-	62.5 mg
Xylitol[3]	390 mg	-	-	-	389 mg
Sucrose[4]	-	391 mg	-	-	-
Inulin[5]	-	-	390 mg	-	-
Isomalt[6]	-	-	-	390 mg	-
Polyvinyl-pyrrolidone VA64	36.40 mg	-	-	-	45.50 mg
Inulin[5]	-	-	24.00 mg	24.00 mg	-
Maltodextrin[7]	-	31.00 mg	-	-	-
Remaining Ingredients					
Vitamin D_3[8]	4.4 mg	4.4 mg	4.4 mg	4.4 mg	4.4 mg
Lemon Flavour	53.2 mg	52.6 mg	52.6 mg	52.6 mg	52.6 mg
Anhydrous Citric Acid	8.0 mg	-	-	-	-
Malic Acid	-	8.0 mg	8.0 mg	8.0 mg	8.0 mg
Aspartame	-	-	1.0 mg	1.0 mg	-
Magnesium Stearate	8.0 mg	8.0 mg	8.0 mg	8.0 mg	8.0 mg
Tablet Weight	1750 mg	1745 mg	1738 mg	1738 mg	1820 mg

[1] Scoralite 1A + 1B
[2] Novasoy 400
[3] CM 50
[4] Tate & Lyle
[5] Raftiline ST
[6] Isomalt PF
[7] Lycatab DSH
[8] 100 CWS

In Examples 10 and 11, additional oligosaccharide (e.g. inulin or oligofructose) may be added to bring the oligosaccharide content to 1 to 5 g per dosage.

EXAMPLE 13

Calcium Carbonate Characteristics

Different samples (lots) of Scoralite 1B and Scoralite 1A + 1B were investigated for particle size (using Malvern Particle size analysis performed on a Malvern Mastersizer S long bench apparatus and a Malvern Mastersizer 2000), specific surface area (BET analysis by nitrogen adsorption performed on a Sartorius micro balance) and apparent bulk density (using apparent bulk density before settling (poured density) according to Ph. Eur., 3rd Edition, 1977). The values determined were as follows:

Scoralite Sample	1B	1B	1B	1A+1B	1A+1B	1A+1B
Apparent bulk density (g/mL)	1.09	1.04	1.02	0.95	0.99	0.89
D(v,0.5) µm	15.1	14.7	15.9	13.3	13.7	11.8
D(v,0.1) µm	8.8	8.7	8.1	6.3	6.5	3.9
D(v,0.9) µm	24.3	23.4	27.8	23.5	24.2	23.0
Specific surface area (m^2/g)	0.5	0.5	0.5	0.4	0.5	0.7

Claims:

1. A process for the preparation of an orally administrable calcium composition, said process comprising the steps of:

(i) obtaining a physiologically tolerable particulate calcium compound having a mean particle size in the range 3 to 40μm, having a crystalline structure and having a surface area of 0.1 to 1.2 m^2/g;

(ii) mixing said calcium compound with a water-soluble diluent and an aqueous solution of a water soluble binder in a fluid bed granulation apparatus and drying the resulting mixture to produce a first granulate;

(iii) optionally mixing said first granulate with one or more further components to produce a second granulate; and

(iv) optionally compressing said first or second granulate to form tablets.

2. A process as claimed in claim 1 wherein said calcium compound is selected from calcium carbonate, calcium lactate, calcium gluconate, calcium citrate, calcium glycerophosphate, calcium phosphate, calcium hydrogen phosphate, calcium glucuronate, calcium aspartate, calcium glucoheptonate and mixtures of two or more thereof.

3. A process as claimed in claim 1 wherein said calcium compound is calcium carbonate.

4. A process as claimed in any one of claims 1 to 3 wherein said calcium compound makes up 68 to 80% wt. of said first granulate.

5. A process as claimed in any one of claims 1 to 4 wherein said calcium compound makes up 60 to 95% wt. of

said second granulate.

6. A process as claimed in any one of claims 1 to 5 wherein in step (i) the same material is used as said diluent and as said binder.

7. A process as claimed in any one of claims 1 to 6 wherein said water-soluble diluent comprises at least one sweetener.

8. A process as claimed in claim 7 wherein said sweetener is selected from sorbitol, xylitol, isomalt, mannitol, sucrose, fructose, maltodextrin, inulin and oligofructose.

9. A process as claimed in any one of claims 1 to 8 wherein said water-soluble diluent makes up 70 to 96% wt. of the total weight of said water-soluble diluent and said water-soluble binder in said first granulate.

10. A process as claimed in any one of claims 1 to 9 wherein said water-soluble binder is selected from celluloses, polysaccharides, maltodextrin, inulin and polyvinylpyrrolidone.

11. A process as claimed in any one of claims 1 to 10 wherein said water-soluble binder is a polyvinylpyrrolidone.

12. A process as claimed in any of claims 1 to 11 wherein said first granulate has a particle size distribution of D(V, 0.1) = 15-21 μm, D(V, 0.5) = 70-120 μm and D(V,0.9) = 190-330 μm.

13. A process as claimed in any one of claims 1 to 12 wherein a said further component is mixed with said first granulate, said further component being selected

from: vitamin B_6, vitamin K, vitamin C, vitamin D, isoflavones, inulin, and oligofructose and mixtures of two or more thereof.

14. A process as claimed in any one of claims 1 to 13 wherein in step (ii) said calcium compound is also mixed with isoflavones.

15. A granulate comprising a fluid bed granulation granulate product of a physiologically tolerable calcium compound, a water-soluble binder and a water-soluble diluent, said calcium compound having a mean particle size in the range 3 to 40μm, having a crystalline structure and having a surface area of 0.1 to 1.2 m^2/g.

16. A granulate as claimed in claim 15 further comprising a lubricant.

17. A granulate as claimed in either of claims 15 and 16 wherein said calcium compound is selected from calcium carbonate, calcium lactate, calcium gluconate, calcium citrate, calcium glycerophosphate, calcium phosphate, calcium hydrogen phosphate, calcium glucuronate, calcium aspartate, calcium glucoheptonate and mixtures of two or more thereof.

18. A granulate as claimed in any one of claims 15 to 17 said diluent is a sweetener selected from sorbitol, xylitol, mannitol, sucrose, fructose, maltodextrin, inulin and oligofructose.

19. A granulate as claimed in any one of claims 15 to 18 wherein said water-soluble binder is selected from celluloses, polysaccharides, maltodextrin, inulin and polyvinylpyrrolidone.

20. A granulate as claimed in any one of claims 15 to

19 comprising a further component selected from: vitamin B_6, vitamin K, vitamin C, vitamin D, isoflavones, inulin, and oligofructose and mixtures of two or more thereof.

21. A tablet comprising a compressed granulate as claimed in any one of claims 15 to 20 containing: calcium carbonate; vitamin D_3; a lubricant; citric acid; and an oligosaccharide.

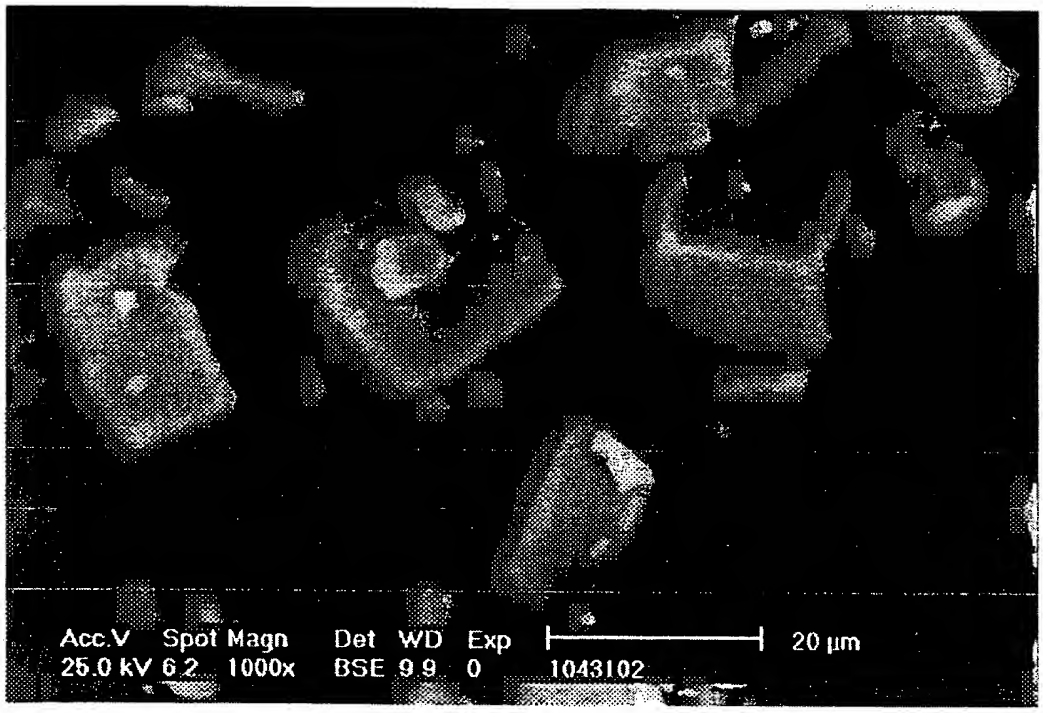

FIG. 1

SCORALITE 1B

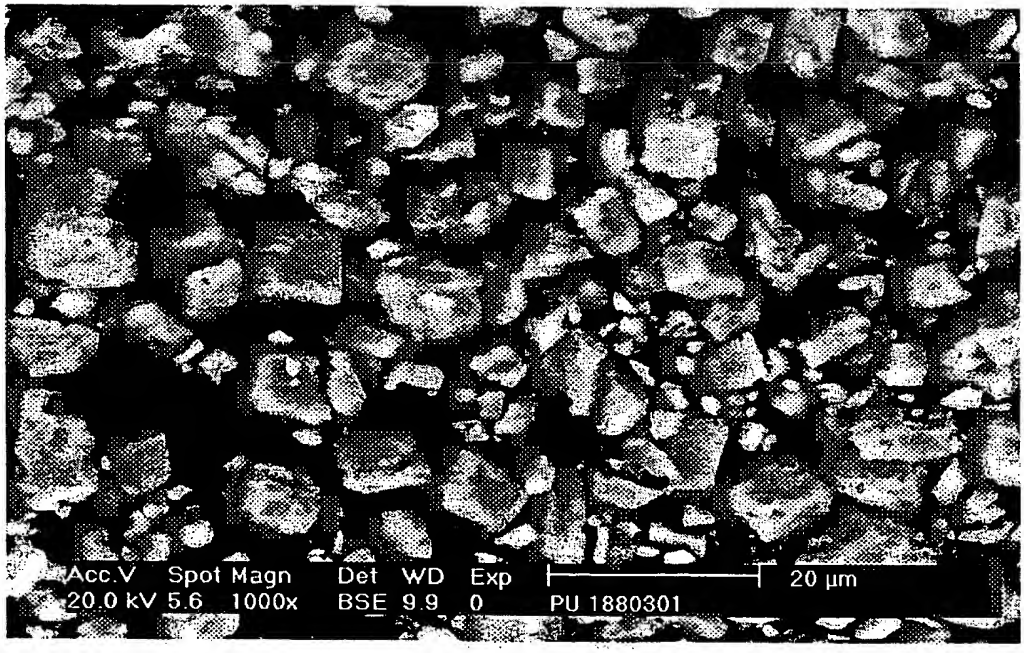

FIG. 2

SCORALITE 1A

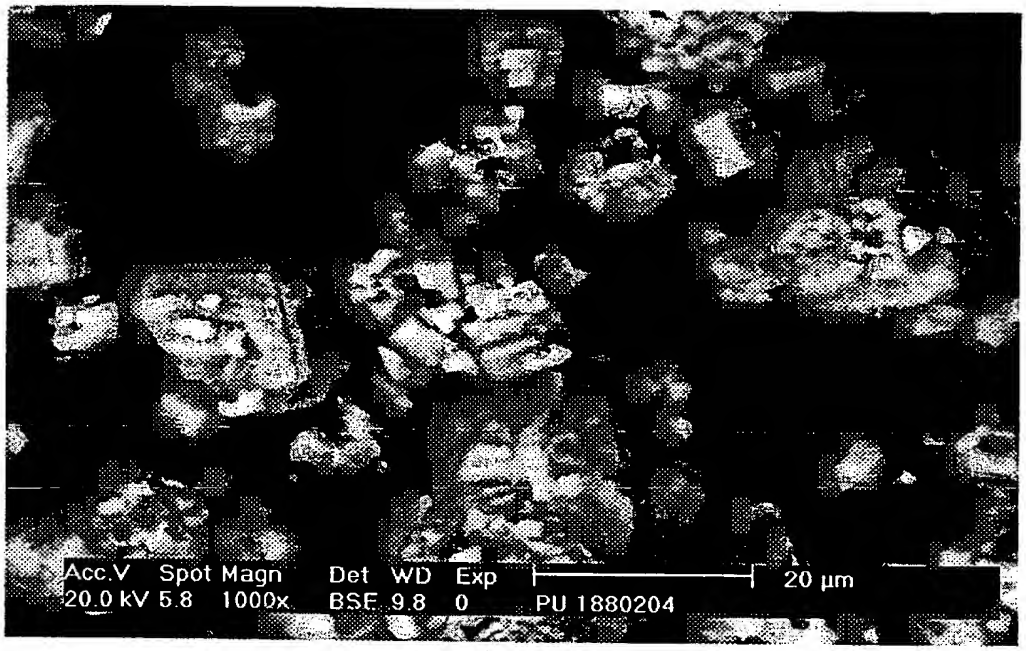

FIG. 3

SUPER-PURITY $CaCO_3$

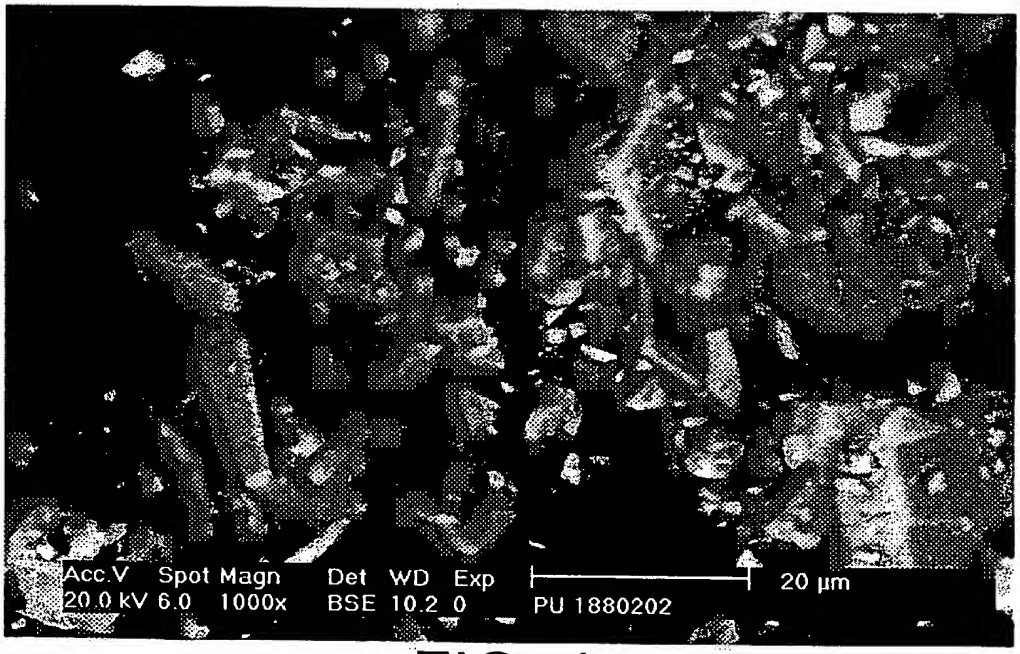

FIG. 4

MEDICINAL HEAVY $CaCO_3$

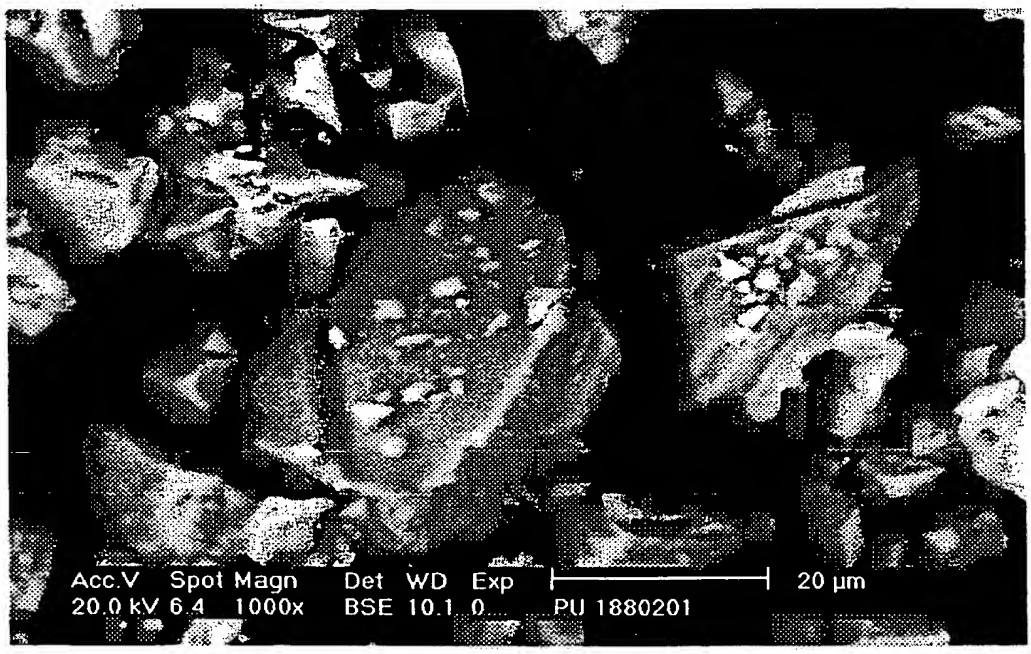

FIG. 5

PHARMA CARB LL

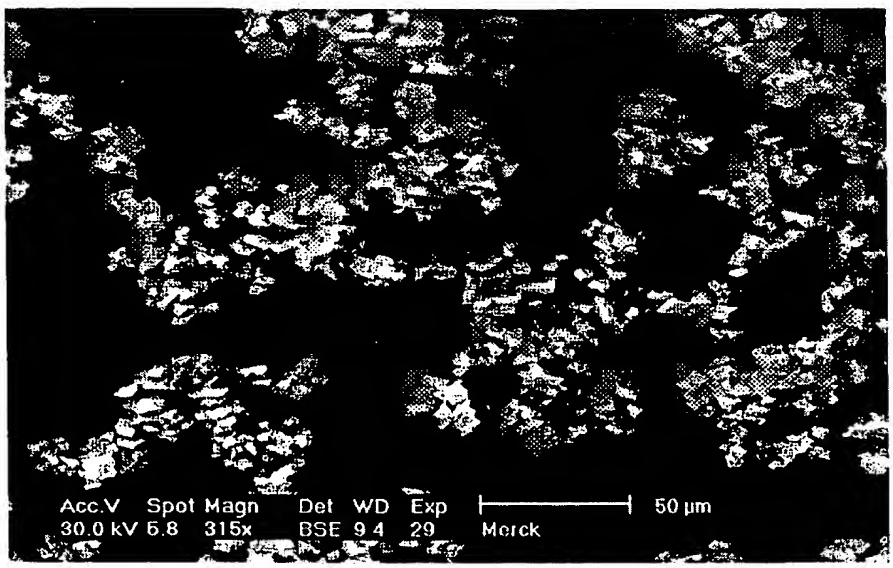

FIG. 6

MERCK 2064

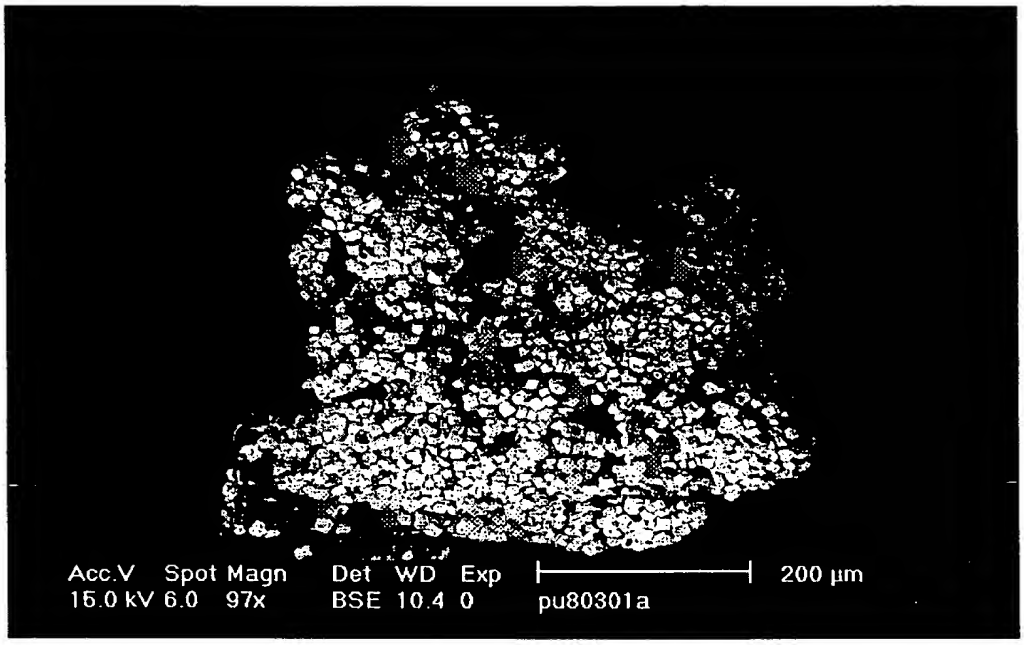

FIG. 7A
SCORALITE 1B

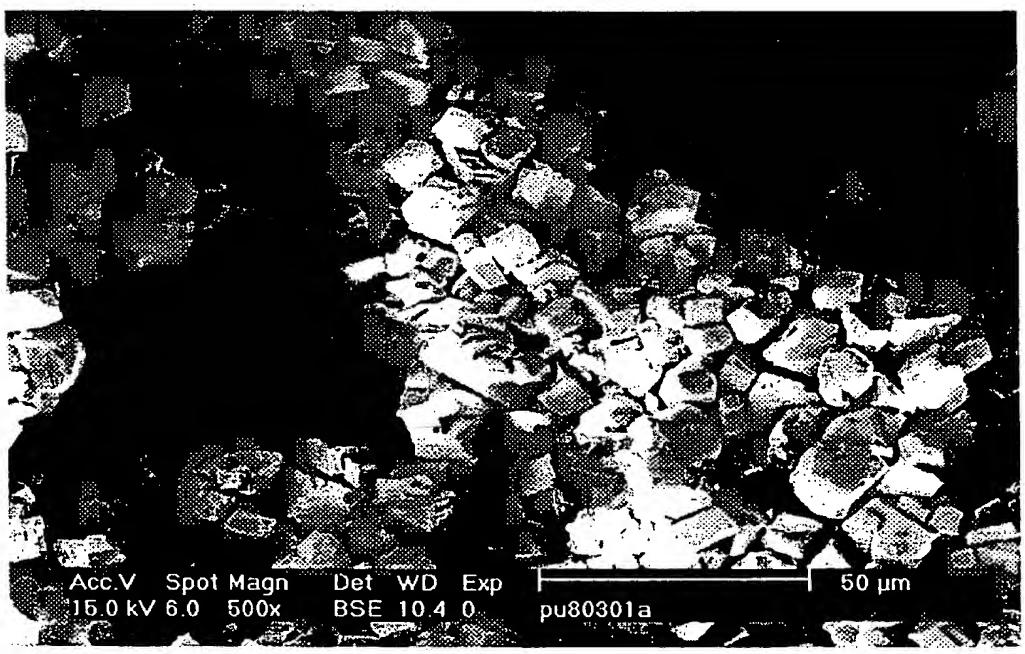

FIG. 7B
SCORALITE 1B

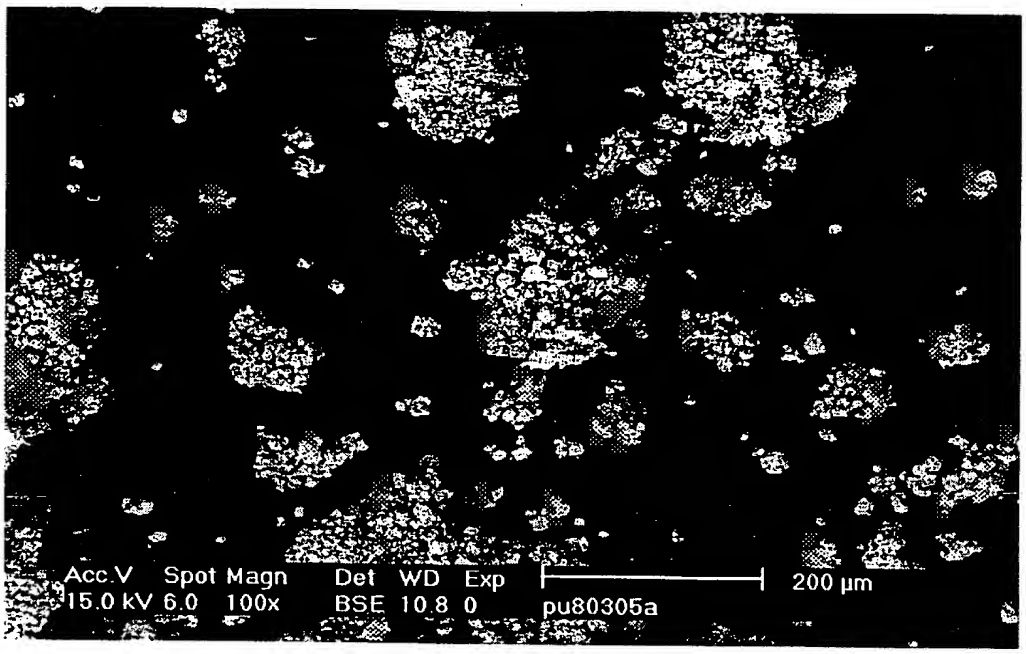

FIG. 8A

SUPER PURITY $CaC0_3$

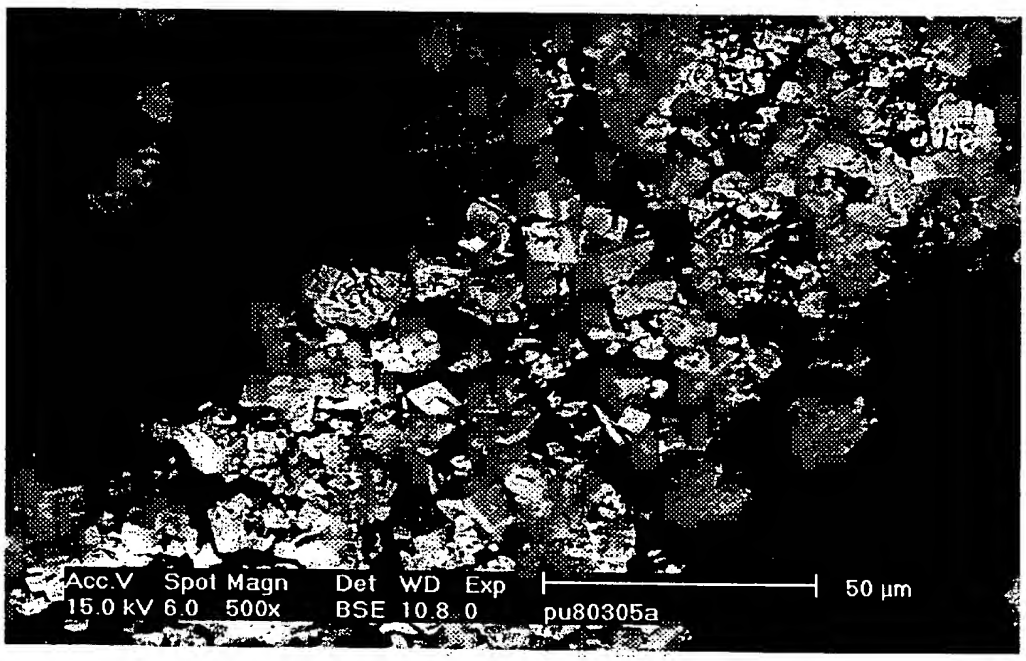

FIG. 8B

SUPER PURITY $CaC0_3$

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/03666

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 192 460 A (DYNAGRAN) 27 August 1986 (1986-08-27) claims 1-25 page 29; example 13	1-4, 6-11, 15-18
Y	FR 2 724 844 A (LABORATOIRE INNOTHERA) 29 March 1996 (1996-03-29) claims 1-8 page 3; example 1	1-21
Y	DE 196 17 487 A (MERCK) 6 November 1997 (1997-11-06) claims 1,2,5,7 page 3, line 43 - line 45 example 1	1-21

-/--

[X] Further documents are listed in the continuation of box C.

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1 February 2000	10/02/2000

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 487 774 A (BASF) 3 June 1992 (1992-06-03) claim 1 page 1, line 47 - line 49	1-21
P,A	EP 0 931 549 A (GERGELY, GERHARD) 28 July 1999 (1999-07-28) the whole document	1-21
A	DATABASE WPI Section Ch, Week 199311 Derwent Publications Ltd., London, GB; Class A,Page 96, AN 1993-088592 XP002129448 & JP 05 032554 A (TEIJIN), 9 February 1993 (1993-02-09) abstract	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/03666

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 192460 A	27-08-1986	US 4684534 A	04-08-1987
		AT 66368 T	15-09-1991
		AU 584674 B	01-06-1989
		AU 5377286 A	28-08-1986
		CA 1256028 A	20-06-1989
		DE 3680930 A	26-09-1991
		JP 2540131 B	02-10-1996
		JP 61225119 A	06-10-1986
FR 2724844 A	29-03-1996	AT 177319 T	15-03-1999
		AU 3168395 A	09-04-1996
		CA 2200568 A	28-03-1996
		DE 29521515 U	05-06-1997
		DE 69508263 D	15-04-1999
		DE 69508263 T	04-11-1999
		EP 0785769 A	30-07-1997
		ES 2131845 T	01-08-1999
		FI 971188 A	20-05-1997
		WO 9609036 A	28-03-1996
		HU 77702 A	28-07-1998
		JP 10505850 T	09-06-1998
		NO 971356 A	21-03-1997
		PL 319585 A	18-08-1997
DE 19617487 A	06-11-1997	CN 1216919 A	19-05-1999
		WO 9741835 A	13-11-1997
		EP 0904059 A	31-03-1999
EP 487774 A	03-06-1992	AT 113202 T	15-11-1994
		DE 69013689 D	01-12-1994
		DE 69013689 T	02-03-1995
		DK 487774 T	21-11-1994
EP 931549 A	28-07-1999	NONE	
JP 5032554 A	09-02-1993	JP 2702325 B	21-01-1998

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(72) Erfinder; und
(75) Erfinder/Anmelder *(nur für US)*: SCHWARZ, Eugen [DE/DE]; Weserstrasse 16, D-64625 Bensheim (DE). MÖSCHL, Gernot [DE/DE]; Falltorstrasse 20, D-64331 Weiterstadt (DE). TALLAVAJHALA, Siva [IN/US]; 8 Langhans Court, Dix Hills, NY 11746 (US).

(74) Gemeinsamer Vertreter: MERCK PATENT GMBH; Frankfurter Strasse 250, Postfach, D-64271 Darmstadt (DE).

(81) Bestimmungsstaaten: CA, CN, CZ, HU, JP, KR, LT, LV, RU, SG, SI, US, europäisches Patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: IMPROVEMENT IN THE TASTE OF ACTIVE PHARMACEUTICAL INGREDIENTS

(54) Bezeichnung: GESCHMACKSVERBESSERUNG VON ARZNEIMITTELWIRKSTOFFEN

(57) Abstract

The invention relates to a process for improving the taste of solid formulations containing one or more active ingredients.

(57) Zusammenfassung

Die Erfindung betrifft ein Verfahren zur Verbesserung des Geschmacksbildes von festen Formulierungen, welche einen oder mehrere Wirkstoffe enthalten.

LEDIGLICH ZUR INFORMATION

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EE	Estland	**LR**	Liberia	**SG**	Singapur		

Geschmacksverbesserung von Arzneimittelwirkstoffen

Die Erfindung betrifft ein Verfahren zur Verbesserung des Geschmacksbildes von festen Formulierungen, wie z. b. von wirkstoff- oder mineralstoffhaltigen Tabletten, und zwar sowohl des eigentlichen Geschmacks selbst als auch des sensorischen Empfindens im Mund.

Polyole und Polyolmischungen werden in großem Umfang als nicht Karies hervorrufende Zusatzstoffe und Trägerstoffe unter anderem für pharmazeutisch Wirkstoffe, Kau- und Lutschtabletten und andere Produkte der Pharmaindustrie und als Komprimate in der Lebensmittelindustrie verwendet. Gewonnen werden Polyole in der Regel durch Hydrierung der ihnen zugrundeliegenden Zucker. In fester Form können sie sowohl durch Kristallisation als auch durch Sprühtrocknung erhalten werden. Der besondere Vorteil einiger Polyole liegt darin, daß sie auch zum direkten Verpressen ohne weitere Hilfs- und Zusatzstoffe geeignet sind.

Die bekannten Polyole, Mannit, Lactit, Isomalt und Xylit sind gering hygroskopisch, zeigen jedoch schlechtes Tablettierverhalten, was sich in geringer Tablettenhärte, Deckeln und hohem Abrieb der Tabletten bemerkbar macht. Grundsätzlich werden hohe Tablettenhärten angestrebt, da in festen Formulierungen Trägerstoffe häufig nur in geringen Mengen eingesetzt werden und Wirkstoffe die Tablettenhärten drastisch vermindern können, so daß eine gegebene Rezeptur nicht tablettierbar ist.

Während Lactit, Isomalt und Xylit in der Komprimatherstellung eher ungebräuchlich sind, wird Mannit in pharmazeutischen Formulierungen durchaus verwendet.

Der Einsatz von Mannit stellt jedoch einen erhöhten Arbeitsaufwand dar, da er in der Regel vor dem Verpressen mit den übrigen Bestandteilen der Rezeptur naßgranuliert werden muß. Erhältlich ist im Handel auch direkt tablettierbarer Mannit, mit dem sich jedoch nur unbefriedigende Härten erzielen lassen, verglichen mit denen bei Verwendung von Sorbit.

Mit Sorbit, insbesondere durch Sprühtrocknung hergestellt, werden sehr gute Tablettenhärten erhalten. Gleichzeitig weisen die hergestellten Komprimate besonders glatte Oberflächen auf. Aus einer Veröffentlichung von Basedow et. al. ist bekannt, daß Calciumcarbonat-haltige Tabletten durch Verpressen mit sprühgetrocknetem oder kristallinem Sorbit hergestellt werden können. Jedoch ist die Hygroskopizität von Sorbit höherer als die anderer Polyole. Dadurch ist seine Verwendbarkeit eingeschränkt. Auch ist in diesem Zusammenhang kein Hinweis in der Literatur zu finden, daß durch Sorbit oder ein anderes Polyol das Geschmacksbild einer Formulierung wesentlich verbessert werden könnte.

Bei der Formulierung oral zu verabreichender pharmazeutischer Zusammensetzungen bereitet in vielen Fällen nicht nur bei flüssigen Applikationsformen das vom Verwender empfundene Geschmacksbild Probleme. Insbesondere beim Kauen von Antacidum-Tabletten wird ein kreidiger Geschmack als unangenehm empfunden. Es wurde bislang wenig erfolgreich durch verschiedenste Zusatzstoffe versucht, diesen kreidigen Geschmack zu überdecken. Bekannte Antacida wiederum vermitteln im Mund einen unerwünschten kreidigen, seifigen Geschmack, der durch herkömmliche Zusatzstoffe nur schwach gemildert werden kann, jedoch beim Kauen weitgehend wieder auftritt.

Als problematisch hat sich auch bei verschiedensten Wirkstoffen ein als äußerst bitter empfundener Geschmack erwiesen. Eine Maskierung besonders bitterer oder kreidiger Wirkstoffe ist bisher auch durch den Zusatz von Geschmacks- oder Aromastoffen nicht gelungen. Es besteht zwar die Möglichkeit, entsprechende Wirkstoffe enthaltende Tabletten mit einem Überzug zu versehen, diese Methode ist jedoch ungeeignet, wenn eine schnelle Aufnahme des Wirkstoffs, die bereits beim Kauen der Tabletten über die Mundschleimhaut erfolgt, angestrebt wird.

Besondere Anforderungen werden auch an die Oberfläche von Tabletten gestellt, die gelutscht werden sollen, wie beispielsweise Halstabletten. Erwünscht ist hierbei eine glatte Oberfläche der eigentlichen Tablette, die während des Lutschens erhalten bleibt und sich nicht nach und nach aufrauht.

Weiterhin werden heute im Bereich der Nahrungsergänzung (Vitamin- und Mineralstoffsupplementierung) vermehrt Lutsch- und vor allem Kautabletten angeboten. Insbesondere bei Tabletten zur Mineralstoffanreicherung ist der Trägeranteil sehr gering, so daß das Geschmacksbild weitgehend vom entsprechenden Mineralstoff geprägt ist.

Des weiteren versucht man, bei der Herstellung von festen Formulierungen zunehmend direkt verpreßbare Wirkstoffe (DC-Wirkstoffe) einzusetzen, um Produktionskosten zu senken.

Aufgabe dieser Erfindung ist es daher, ein Verfahren zur Verfügung zu stellen, wodurch einerseits das Geschmacksbild von festen Formulierungen verbessert wird, gleichzeitig aber auch das sensorische Mundgefühl der hergestellten Produkte vorteilhaft beeinflußt wird.

Es wurde nun gefunden, daß das Geschmacksbild von festen Formulierungen verbessert werden kann, indem eine einen oder mehrere Wirkstoffe enthaltende Zusammensetzung, erhältlich durch Co-Sprühtrocknung bzw. Wirbelschichtgranulation mit mindestens einem Polyol, durch Verpressen in einer festen Darreichungsform hergestellt wird.

Gegenstand der Erfindung ist somit ein Verfahren zur Herstellung von DC-Wirkstoffen, die zur Verbesserung des Geschmacksbildes von festen Formulierungen, welche einen oder mehrere Wirkstoffe enthalten, beitragen, dadurch gekennzeichnet, daß man eine einen oder mehrere Wirkstoffe enthaltende Zusammensetzung, erhältlich durch Co-Sprühtrocknung bzw. Wirbelschichtgranulation mit mindestens einem Polyol, durch Verpressen in einer festen Darreichungsform herstellt. Die eingesetzte Gesamtmenge Polyol ist dabei so zu wählen, daß in dem nach dem erfindungsgemäßen Verfahren hergestellten pulverförmige Substanzgemisch 10 bis 90 Gew.-%, insbesondere 25 bis 75 Gew.-% enthalten sind.

Die erfindungswesentliche Zusammensetzung ist dabei erhältlich durch Lösen von mindestens einem Polyol in Wasser und Lösen oder Suspendieren mindestens eines Wirkstoffs in einem Lösungsmittel und Versprühen des erhaltenen wäßrigen Gemischs in einem Luft-

strom mit einer Temperatur von 120 bis 300 °C, vorzugsweise 140 bis 190 °C. Es ist aber auch möglich das erhaltene wäßrige Gemisch in einem Luftstrom mit einer Temperatur von 40 bis 120 °C zu verwirbeln.

Dem wäßrigen Gemisch können vor der Co-Sprühtrocknung oder Wirbelschichtgranulation geschmackskorrigierende Substanzen und gegebenenfalls Farbstoffe hinzugefügt sein. Als geschmackskorrigierende Substanzen kommen u. a. natürliche oder synthetische Süßstoffe aus der Gruppe Saccharin, Aspartam®, Acesulfam K, Neohesperidin DC, Sucralose, Thaumatin oder Steviosid in Frage. Als Polyole sind solche aus der Gruppe Sorbit, Mannit, Lactit, Isomalt, Maltit Erythrit oder Xylit einsetzbar. Diese können in einer Menge von 10 bis 90 Gew.-%, insbesondere 25 bis 75 Gew.-% im hergestellten Produkt enthalten sein.

Gegenstand der Erfindung sind somit auch die durch das erfindungsgemäße Verfahren hergestellten festen Formulierungen mit verbessertem Geschmacksbild. In diesen Formulierungen können einerseits Mineralstoffe aus der Gruppe physiologisch verträglicher Ca-, Mg-, Na-, K-, Fe- und Zn-Salze in einer Menge von 0,1 bis 90 Gew.-%, insbesondere von 25 bis 75 Gew.-%, gegebenenfalls Spurenelemente, sowie ein oder mehrere Vitamin(e) und gegebenenfalls ein oder mehrere eventuell bitter schmeckende Wirkstoffe enthalten sein.

In den nach dem erfindungsgemäßen Verfahren hergestellten Formulierungen können ein oder mehrere pharmazeutische Wirkstoffe enthalten sein. Solche Wirkstoffe können unter anderem sein Antacida, Antiallergika, Analgetika, Hormone, Steroide, Östrogene, Kontrazeptiva, nasale Dekongestionsmittel, H_1- und H_2-Antagonisten, $ß_2$-Stimulantien, Vasodilatoren, Antihypertensiva, infektionsvorbeugende Mittel, Laxantien, Antitussiva, Bronchodilatoren, Mittel gegen Halsschmerzen, Wismut und seine Salze, Pilzmittel, Antibiotika, Stimulanzien (wie z. B. Amphetamine) Alkaloide, orale Hypoglycaemica, Diuretica, Cholesterin senkende Mittel, Kombinationen verschiedener pharmazeutisch wirksamer Mittel oder andere. Diese Wirkstoffe können in einer Menge von 0,1 bis 70 Gew.-% enthalten sein.

Die Wirkstoffe können als beschichtete T ilchen, Liposomen oder Mikropartikel vorliegen. Als Beschichtung können übliche, in der Pharmazie verwendete Substanzen dienen. Die Teilchengröße der Wirkstoffe beträgt vorzugsweise 0,1 bis 800 µm mit einer Schüttdichte von 0,15 bis 1 g/cm^3.

Natürlich sind die im vorhergehenden Text gegebenen Gew.-%-Angaben so zu verstehen, daß die Wahl der Gewichtsprozente der eingesetzten Substanzen in der Summe 100 nicht übersteigen.

Der Begriff Polyol steht für Zuckeralkohole der allgemeinen Formel

$CH_2OH-(CHOH)_n-CH_2OH$,

wobei n für 2 bis 6, vorzugsweise 3 bis 4, steht,

sowie deren dimere Anhydride, insbesondere $C_{12}H_{24}O_{11}$.

Insbesondere steht der Begriff Polyole für Hexite wie Sorbit und Mannit, Pentite wie Xylit, möglich sind aber auch C_4-Polyalkohole wie Erythrit oder C_{12}-Polyalkohole wie Lactit oder Maltit. Der Begriff Polyole steht aber auch für geeignete Kohlehydrate.

Zur Sprühtrocknung wird eine wäßrige Lösung von mindestens einem Polyol verwendet. Der Feststoffgehalt wird zuvor vorzugsweise durch Mischen bei einer Temperatur von bis 80 ° C mindestens einer Polyol-Lösung mit einer oder mehrerer Lösungen oder Suspensionen des oder der gewünschten Wirkstoffe im gewünschten Verhältnis auf etwa 10 - 90 Gew.-%, insbesondere 50 bis 72 Gew.-% eingestellt. Die Versprühung wird durch Zerstäuben mittels Düsen, vorzugsweise mittels eines Zentrifugalzerstäubers, in einem auf eine Temperatur von 120 bis 300 °C, vorzugsweise 140 bis 190 °C erwärmten, trockenen, zentrifugal eingeblasenen Luftstrom durchgeführt. Die Menge der zugeführten Polyollösung und der eingeblasenen Heißluft wird so abgestimmt, daß das erhaltene pulverförmige Substanzgemisch bis auf einen Wassergehalt von etwa 0,1 bis etwa 1 Gew.-%, gegebenenfalls im Fließbett, getrocknet wird. Auf jeden Fall sollte der Wassergehalt unterhalb 1 Gew.-% liegen.

Die Wirbleschichtgranulation wird, wie z. B. in P. Grassmann, F. Widmer „ Einführung in die thermische Verfahrenstechnik" beschrieben, durchgeführt.

Aufgrund der besonderen Herstellungsart durch Versprühen einer wäßrigen Lösung ist es möglich, nicht wasserlösliche und wasserlösliche Zusätze, wie z. b. Zitronensäure, Süßstoffe, insbesondere Acesulfam K, Aspartam®, Saccharin, Cyclamat, Sucralose, Neohesperidin DC, Farbstoffe sowie pharmazeutische Wirkstoffe, wie z. B. Analgetika, Antacida und dergleichen, Vitamine und gegebenenfalls Spurenelemente homogen in den erfindungsgemäßen Zusammensetzungen, bzw. festen Formulierung und den daraus hergestellten Tabletten zu verteilen.

Die gegebenenfalls zuzusetzenden Bindemittel sind dem Fachmann geläufig und dienen der Erhöhung der Festigkeit der Zusammensetzung. Als Bindemittel bevorzugt sind Cellulose-Derivate, insbesondere Hydroxypropylmethylcellulose, Carboxymethylcellulose oder Stärke.

Die so charakterisierten Polyol-Zusammensetzungen besitzen eine Reihe von vorteilhaften Tablettiereigenschaften:

Überraschenderweise kann festgestellt werden, daß durch das erfindungsgemäße Verfahren unter Verwendung der erfindungsgemäßen Zusammensetzungen feste Formulierungen, insbesondere Tabletten, mit einem erheblich verbesserten Geschmacksbild und sensorischem Mundgefühl erhalten werden. Gleichzeitig sind diese vorteilhaften Eigenschaften mit der Möglichkeit verbunden, die durch Co-Sprühtrocknung bzw. Wirbelschichtgranulation erhaltenen Zusammensetzungen direkt zu verpressen. Es handelt sich dabei also um direkt verpreßbare Wirkstoffformulierungen (DC-Wirkstoffe).

Bei Verwendung von Formulierungen mit einem hohen Mineralstoffgehalt von bis zu 90 Gew.-% werden einerseits drastisch verbesserte Tablettiereigenschaften gefunden, andererseits sind die hergestellten Tabletten während des Verpackungsvorgangs durch einen wesentlich geringeren Abrieb gekennzeichnet. Auch werden bei Verwendung der erfindungsgemäßen Zusammensetzungen bei gleicher Preßkraft, wie

sie bei bekannten polyolhaltigen Formulierungen angelegt wird, härtere Tabletten mit glatteren Oberflächen erhalten. Dieses anfänglich empfundene verbesserte sensorische Gefühl im Mund wird auch beim Kauen oder Lutschen empfunden, da der sonst übliche kreidige, oder gegebenenfalls seifige Geschmack weitestgehend überdeckt ist. Überraschender Weise wird jedoch nicht nur das Geschmacksbild dieser Mineralstofftabletten verbessert. Auch Formulierungen, in die äußerst bitter schmeckende Wirkstoffe eingearbeitet sind, werden als wesentlich wohlschmeckender empfunden, da der Bittergeschmack nicht mehr so extrem durchschlägt.

Die nachfolgenden Beispiele dienen der besseren Veranschaulichung der beschriebenen und beanspruchten Erfindung, sind jedoch nicht zur Einengung des Schutzbereichs auf diese Beispiele geeignet.

Beispiele

Beispiel 1

Antacidum-Tablette

Zusammensetzung der Tablettiermischung:

Calciumcarbonat	65,50 %
Karion Instant	28,19 %
Karion Pulver P300	4,70 %
Chlorophyllin 100 %	0,01 %
Neohesperidin DC	0,10 %
Pfefferminzaroma Naefco (Fa. Firmenich)	0,30 %
Mg-Stearat	1,00 %

Mechanische Herstellung der Mischung:

Calciumcarbonat und Sorbit (Karion Instant und Karion Pulver P300) werden in einem Turbulamischer 5 Minuten gemischt. Anschließend wird Chlorophyllin, Neohesperidin DC und das Pfefferminzaroma zugegeben und weitere 5 Minuten gemischt. Die Mischung wird durch ein Sieb mit einer Porenweite von 1 mm gegeben. Über die gesiebte Mischung wird Magnesiumstearat durch ein Sieb, das eine Porenweite von 250 µm aufweist, aufgesiebt und erneut 5 Minuten gemischt. Die so erhaltene Mischung wird tablettiert.

Herstellung der Mischung durch Co-Versprühen:

Calciumcarbonat, Sorbit, Neohesperidin DC und Chlorophyllin werden in der vorher genannten Weise cogesprüht. Das cogesprühte Material und das Aroma werden im Turbulamischer vorgelegt, Magnesiumstearat über ein Sieb, das eine Porenweite von 250 µm aufweist, aufgesiebt und 5 Minuten gemischt. Die so erhaltene Mischung wird tablettiert.

Ergebnisse:

	Mechan. Mischung	Cogesprühtes Material
Tablettierung (qualitativ)	Mischung rieselt sehr schlecht, Matritzenfüllung nicht immer vollständig, Deckeln der Tabletten	einwandfreie Tablettierung
Fließneigungswinkel	37,5°	32,6°
Tablettenhärte	40 N bei 19 KN (max. erzielbare Tablettenhärte)	129 N bei ca. 8 KN
$S_{rel.}$ Tablettengewicht	nicht auswertbar	0,19 %
Abrieb (Roche)	nicht auswertbar	0,37 %
Sensorik	stark kreidiger Geschmack, Mundgefühl stark kreidig, sehr stumpf, Aroma wenig ausgeprägt, da vom kreidigen Geschmack maskiert	gut kaubare Tabletten ohne kreidiges Mundgefühl, Geschmack nur sehr schwach kreidig, Aroma gut erkennbar
Wirkstoff-Verteilung		
Mittelwert (in % vom theoret. Wert)	98,2	99,9
Abweichung (min/max)	96,0 - 99,8	99,6 - 100,2
Abweichung	3,8 %	0,6 %

Beispiel 2

Analgetikum-Tablette

Zusammensetzung des Tablettiermaterials:

Acetylsalicylsäure (ASS)	74,0 %
Sorbit-Anteil	24,5 %
(Instant-Qualität beigemischt, bzw. mit ASS gesprüht)	
Acesulfam K	0,5 %
Magnesiumstearat	1,0 %

Tablettier- und Geschmacksvergleich

Herstellung einer mechanischen Mischung:

ASS wird durch Mahlung fein gepulvert und mit Sorbit Instant im Turbula-Schüttel-Mischer einschließlich des mikronisierten Süßstoffes ASK verrieben. Anschließend erfolgt eine Siebung zur Desagglomeration mit einem 1 mm-Sieb und die Nachmischung mit Magnesiumstearat und anschließend die Tablettierung.

Herstellung von co-gesprühtem Tabletten Material:

Feingepulverte, gemahlene ASS wird teilweise (ca. 5 %) in der Wirbelschicht vorgelegt. und der Rest im Verhältnis von ca. 1 : 1 in Sorbitlösung dispergiert. Die Dispersion wird durch Rühren aufrecht erhalten und mit dem Süßstoff ASK direkt in das Wirbelbett gesprüht, bei gleichzeitiger Wasserverdampfung.

Dem so gebildeten relativ feinen Sprühgranulat wird als Gleitmittel 1 % Magnesiumstearat beigemischt. Die erhaltene Mischung wird direkt tablettiert.

Erg bnisse:

	Mechan. Mischung	Cogesprühtes Material
Aussehen	wenig rieselfähige Mischung, deren beiden Hauptkomponenten erkennbar sind	homogenes, gut rieselfähiges Tablettier-Granulat
Tablettierung: 500 mg Preßkraft 10 kN		
Tablettenhärte:	90 N	210 N
Abrieb (Friab.)	0,6 %	0,3 %
Sensorik	säuredominanter Geschmack, hohe Oberflächenrauheit der Tablette	gemilderter süßsaurer Geschmack, angenehmes Kauverhalten (glatte, wenig saugfähige Oberfläche)

Beispiel 3

Vitamin C-Tablette

Ascorbinsäure	87,7 %
Sorbit	10,0 %
Orangenaroma (pulverförmig)	0,7 %
Acesulfam K	0,6 %
Mg-Stearat	1,0 %

Herstellung einer mechanischen Mischung:

Die feinkristalline Ascorbinsäure wird im Turbula-Schüttelmischer mit Sorbit Instant (Körnung unter 0,3 mm), Süßstoff und Aroma innig verrieben. Danach wird das Gleitmittel Magnesium-Stearat aufgesiebt und eingemischt.

Herstellung von co-g sprühtem Tablettiermat rial:

Ascorbinsäure, Sorbit und Süßstoff werden mit ca. 40 % Feststoffanteil in Wasser bei 40 °C gelöst und auf ein gleichermaßen zusammengesetztes Bett von Kristallkeimen (Anteil an der Gesamtmasse ca. 15 %) im Wirbelgerät aufgesprüht. Das Sprühgranulat wird vor der Tablettierung mit dem gleichen Aroma und Magnesium-Stearat vermischt.

Ergebnisse:

	Mechan. Mischung	Cogesprühtes Material
Aussehen	Sorbitpartikel sind vereinzelt erkennbar	homogenes, gut rieselfähiges Tablettiergranulat
Tablettierung: Menge: 500 mg Preßkraft 20 kN		
Tablettenhärte:	20 N	160 N
Abrieb (Friab.)	22 %	0,2 %
Sensorik	zu weiche Tabletten, rauhe Oberfläche, (nicht akzeptables Ergebnis)	süßsaure Vitamin C-Tablette mit glatter Oberfläche und angenehmen Kaueigenschaften

Patentansprüche

1. Verfahren zur Verbesserung des Geschmacksbildes von festen Formulierungen, welche einen oder mehrere Wirkstoffe enthalten, dadurch gekennzeichnet, daß man eine einen oder mehrere Wirkstoffe enthaltende Zusammensetzung, erhältlich durch Co-Sprühtrocknung bzw. Wirbelschichtgranulation mit mindestens einem Polyol, bzw. Kohlehydrat durch Verpressen in einer festen Darreichungsform herstellt.

2. Verfahren gemäß Anspruch 1 dadruch gekennzeichnet, daß es sich bei den durch Co-Sprühtrocknung bzw. Wirbelschichtgranulation erhaltenen Zusammensetzungen um direkt verpreßbare Wirkstoffformulierungen handelt.

3. Verfahren nach den Ansprüchen 1 - 2 dadurch gekennzeichnet, daß man eine Zusammensetzung verwendet, welche geschmackskorrigierende Substanzen und gegebenenfalls Farbstoffe enthält.

4. Zusammensetzung nach den Ansprüchen 1 - 3, erhältlich durch Lösen von mindestens einem Polyol in Wasser und Lösen oder Suspendieren mindestens eines Wirkstoffs in einem Lösungsmittel und Versprühen des erhaltenen wäßrigen Gemischs in einem Luftstrom mit einer Temperatur von 120 bis 300 °C, insbesondere 140 bis 190 °C.

5. Zusammensetzung nach den Ansprüchen 1 - 4, erhältlich durch Lösen von mindestens einem Polyol in Wasser und Lösen oder Suspendieren mindestens eines Wirkstoffs in einem Lösungsmittel und Verwirbelung des erhaltenen wäßrigen Gemischs in einem Luftstrom mit einer Temperatur von 40 bis 120 °C.

6. Zusammensetzung nach einem oder mehreren der Ansprüche 1 - 5, dadurch gekennzeichnet, daß sie mindestens
   a) einen Wirkstoff,
   b) ein Polyol,
   c) gegebenenfalls einen natürlichen oder synthetischen Süßstoff und
   gegebenenfalls einen Farbstoff enthält.

7. Zusammensetzung nach Anspruch 6, dadurch gekennzeichnet, daß si einen Süßstoff aus der Gruppe Saccharin, Aspartam®, Acesulfam K, Neohesperidin DC, Sucralose, Thaumatin oder Steviosid enthält.

8. Zusammensetzung nach einem oder mehreren der Ansprüche 1 - 7, dadurch gekennzeichnet, daß sie mindestens einen oder mehrere Polyol(e) aus der Gruppe Sorbit, Mannit, Lactit, Isomalt, Maltit, Erythrit oder Xylit enthält.

9. Feste Formulierung mit verbessertem Geschmacksbild, hergestellt nach einem Verfahren gemäß der Ansprüche 1 - 3.

10. Feste Formulierung gemäß Anspruch 9, dadurch gekennzeichnet, daß darin 10 bis 90 Gew.-%, insbesondere 25 bis 75 Gew.-%, Mineralstoffe aus der Gruppe physiologisch verträglicher Ca-, Mg-, Na-, K-, Fe- und Zn-Salze, gegebenenfalls Spurenelemente und gegebenenfalls ein oder mehrere Vitamine, sowie und gegebenenfalls ein oder mehrere eventuell bitter schmeckende Wirkstoffe enthalten sind.

11. Feste Formulierung gemäß Anspruch 9, dadurch gekennzeichnet, daß darin ein oder mehrere Wirkstoffe aus der Gruppe Analgetika, Antacida, Antiallergika, Hormone, Steroide, Östrogene, Kontrazeptiva, nasale Dekongestionsmittel, H_1- und H_2-Antagonisten, $ß_2$-Stimulantien, Vasodilatoren, Antihypertensiva, infektionsvorbeugende Mittel, Laxantien, Antitussiva, Bronchodilatoren, Mittel gegen Halsschmerzen, Wismut und seine Salze, Pilzmittel, Antibiotika, Alkaloide, orale Hypoglycaemica, Diuretica, Cholesterin senkende Mittel enthalten sind.

12. Feste Formulierung gemäß Anspruch 9, dadurch gekennzeichnet, daß darin ein oder mehrere pharmazeutische Wirkstoffe in einer Menge von 0,1 bis 70 Gew-% enthalten sind.

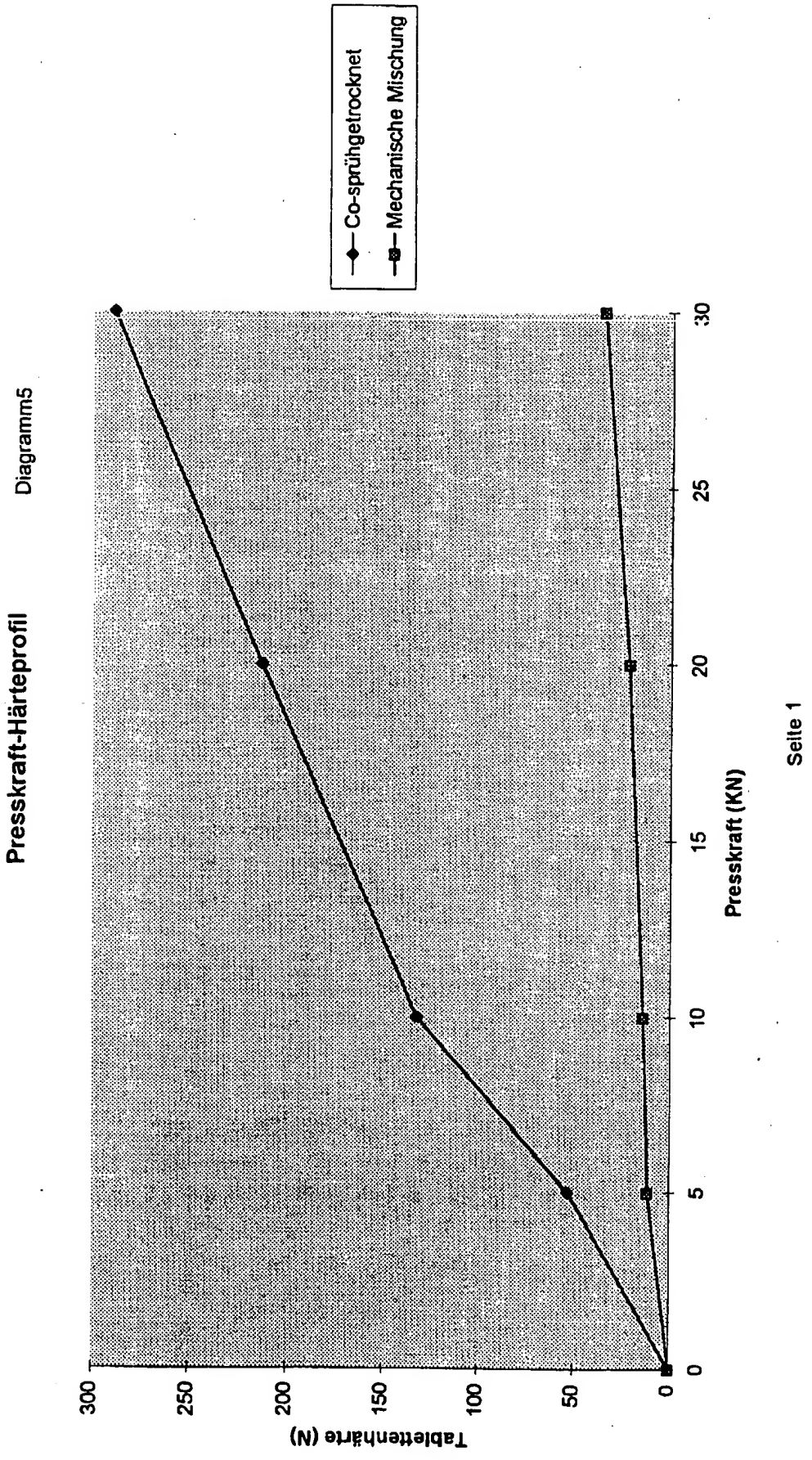
Co-sprühgetrocknet
Mechanische Mischung
Presskraft-Härteprofil
Diagramm5
Tablettenhärte (N)
Presskraft (KN)
Seite 1
0
50
100
150
200
250
300
0
5
10
15
20
25
30

FIG. 1

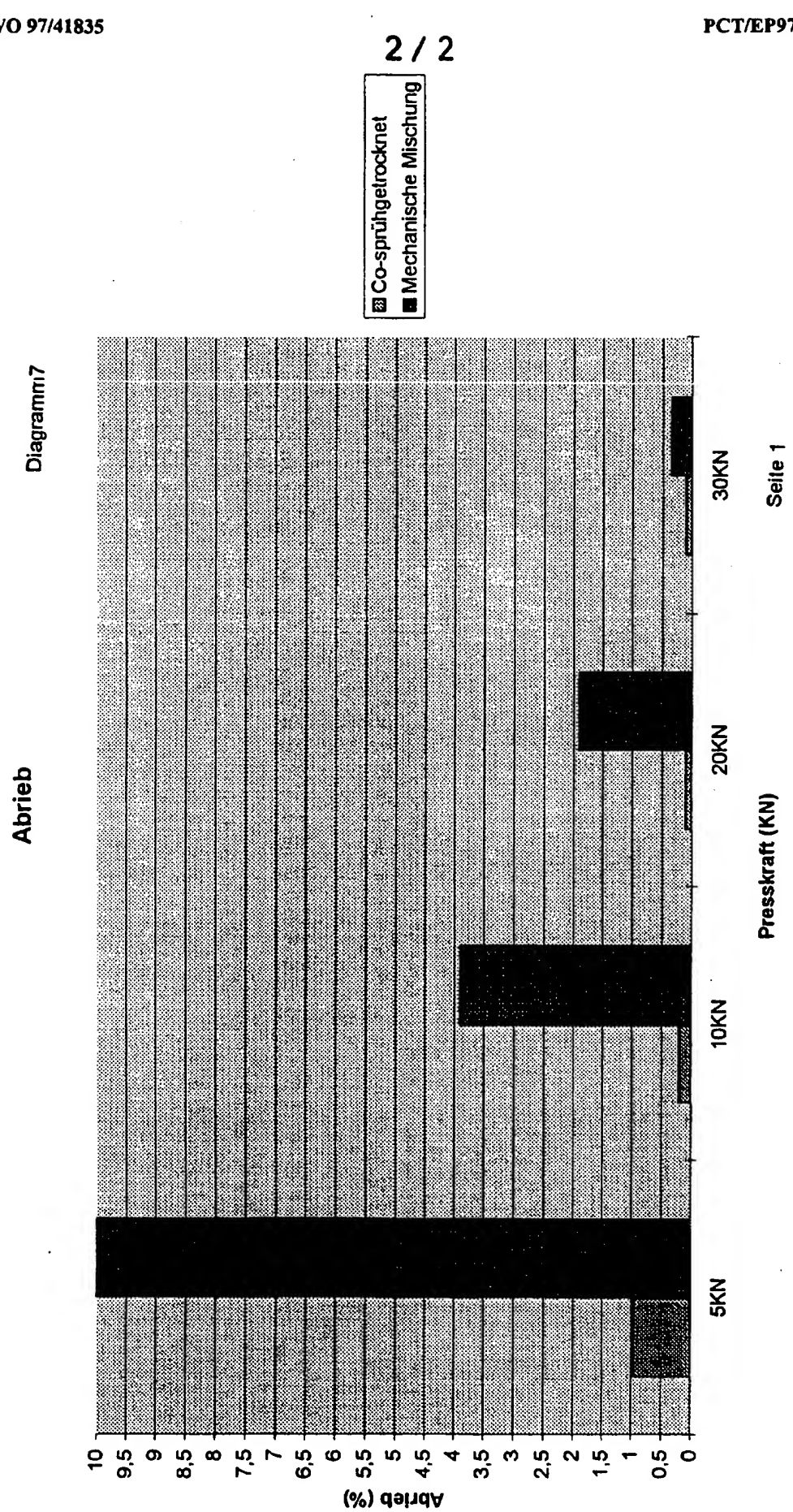
Co-sprühgetrocknet
Mechanische Mischung
Diagramm7
Abrieb
Seite 1
30KN
20KN
10KN
5KN
Presskraft (KN)
Abrieb (%)
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

FIG. 2

INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/EP 97/01781

A. CLASSIFICATION F SUBJECT MATTER
IPC 6 A61K9/14 A61K9/20 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 143 576 A (WARNER LAMBERT) 5 June 1985 see claims 1,9,11,23,26 see page 12; examples 2-5 ---	1,2,4-6, 8,9,11, 12
X	DATABASE WPI Section Ch, Week 9344 Derwent Publications Ltd., London, GB; Class B05, AN 93-348346 XP002042144 & JP 05 255 080 A (TAISHO PHARM.) , 5 October 1993 see abstract --- -/--	1,2,5,8, 9,11,12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
30 September 1997	15. 10. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

Inter .onal Application No
PCT/EP 97/01781

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 892 889 A (PAULA S. KIRK, ET AL.) 9 January 1990 see claims 1,4,6,10 see column 4; example 1 -----	1-3,6,8, 9,11,12

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INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
PCT/EP 97/01781

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 143576 A	05-06-85	CA 1201383 A	04-03-86
		AU 3548484 A	30-05-85
		JP 60123421 A	02-07-85
US 4892889 A	09-01-90	CA 1324576 A	23-11-93

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 97/01781

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 A61K9/14 A61K9/20 A61K9/00

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	EP 0 143 576 A (WARNER LAMBERT) 5.Juni 1985 siehe Ansprüche 1,9,11,23,26 siehe Seite 12; Beispiele 2-5 ---	1,2,4-6, 8,9,11, 12
X	DATABASE WPI Section Ch, Week 9344 Derwent Publications Ltd., London, GB; Class B05, AN 93-348346 XP002042144 & JP 05 255 080 A (TAISHO PHARM.) , 5.Oktober 1993 siehe Zusammenfassung --- -/--	1,2,5,8, 9,11,12

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

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Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
30.September 1997	15. 10. 97

Name und Postanschrift der Internationale Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 97/01781

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	US 4 892 889 A (PAULA S. KIRK, ET AL.) 9.Januar 1990 siehe Ansprüche 1,4,6,10 siehe Spalte 4; Beispiel 1 -----	1-3,6,8, 9,11,12

INTERNATIONALER RECHERCHENBERICHT

Intern. ales Aktenzeichen
PCT/EP 97/01781

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
EP 143576 A	05-06-85	CA 1201383 A	04-03-86
		AU 3548484 A	30-05-85
		JP 60123421 A	02-07-85
US 4892889 A	09-01-90	CA 1324576 A	23-11-93